Is Angina Preventable?

M. F. Oliver

Abstract
Last week I looked through some of the earlier records of the hospital where you, Sir, and I and most of us here had our training. You may like to know that the interest in ischaemic heart disease which Lauder Brunton established 100 years ago is being actively perpetuated in the same ward. The area where we established the first major Coronary Care Unit in Britain a year ago is very probably the same as that where young Brunton made his classical observation concerning the use of nitride of amyl.

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Intervention can be expected to produce the highest yield if it is made before symptoms of ischaemic heart disease develop. That we should direct our attention particularly towards the pre-symptomatic stage of the disease is emphasized by consideration of the immediate mortality following acute myocardial infarction. It has been shown by Bainton and Peterson (1963) and by Kannel et al (1963) that the majority of patients who die after their first myocardial infarct do so within an hour of the onset of symptoms. Thus, many victims never reach hospital and the mortality from acute heart attacks is considerably under-estimated from hospital statistics. These reports highlight the need to prevent the attack from occurring in the first instance, and in this talk I do not propose to consider what can be done about the prevention of angina once a patient has developed myocardial infarction. This is usually known as secondary prevention.

A far more interesting and fundamental challenge is – What can be done towards the primary prevention of angina and other presentations of ischaemic heart disease? Professor Morris has already outlined with great clarity the principal risk factors associated with the development of ischaemic heart disease, and I propose now to return to these and consider which are amenable to control and prevention (Table I on page 44).

Control of risk factors

Hyperlipidaemia is mostly controllable, either by the use of Atromid-S or a polyunsaturated fatty acid diet and I will consider the control of this risk factor in more detail shortly. It may also be partly preventable insofar as a rapid increase in weight is preventable and this is often associated with hypertriglyceridaemia.

The control of hypertension presents a major problem which is outside the scope of this talk. In the first place it is by no means certain, because of the unsatisfactory nature of the available drugs, that hypertension can always be controlled and certainly the side effects of these drugs are sufficiently serious to preclude their widespread use as a means of control of moderate hypertension in otherwise healthy men. In the second place, it has not been shown that adequate control even of severe hypertension is associated with fewer myocardial infarcts when comparison is made with patients whose hypertension has not been adequately controlled (Hodge et al., 1961; Hood et al., 1963). The principal reasons for reduction of overall mortality when hypertension is controlled are that there are fewer deaths from cerebrovascular accidents and from congestive failure, but there is no significant change in the incidence of deaths from ischaemic heart disease.

While most of the remarks which I am making apply equally to myocardial infarction as to angina, it is worth stressing that the pattern of cigarette smoking in patients with angina pectoris is quite different from that which one obtains from patients with myocardial infarction.
TABLE I

RISK FACTORS IN ISCHAEMIC HEART DISEASE AND THEIR CONTROL

Well documented risk factors
- Hyperlipidaemia — controllable, partly preventable
- Hypertension — partly controllable, seldom preventable
- Cigarette smoking — preventable
- Surgical or irradiation menopause — often preventable

Less well documented influences
- Physical inactivity — preventable
- A rapid gain in weight — preventable
- Diabetes mellitus — partly controllable, not preventable
- Hyperuricaemia — partly controllable, not preventable
- Thrombogenic tendency — not controllable, not preventable
- Psychogenic stress — partly controllable, not preventable

TABLE II

SMOKING HABITS IN 118 WOMEN UNDER 45 YEARS WITH CONFIRMED ISCHAEMIC HEART DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Total numbers</th>
<th>Nos. of non-smokers</th>
<th>Nos. of smokers and cigarettes day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-14</td>
</tr>
<tr>
<td>A.P.</td>
<td>58</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>M.I.</td>
<td>60</td>
<td>8</td>
<td>27</td>
</tr>
</tbody>
</table>

Comparison of non-smokers with heavy smokers (15 or more) indicates a significant difference between A.P. and M.I. (0.005 > P > 0.001).

TABLE III

SMOKING HABITS IN 118 WOMEN UNDER 45 YEARS WITH CONFIRMED ISCHAEMIC HEART DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Per cent who are non-smokers</th>
<th>Per cent who are cigarette smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-14/day</td>
<td>15-24/day</td>
</tr>
<tr>
<td>A.P. (58)</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>U.K. population*</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>M.I. (60)</td>
<td>13</td>
<td>45</td>
</tr>
</tbody>
</table>

*Mean figure for women 21–35 and 36–55 derived from 1961 report of Tobacco Manufacturers Committee.
Professor Morris has already mentioned the experience of the Framingham study and I will only add to this by commenting that Doyle et al., (1964) also showed a clear-cut relationship between heavy cigarette smoking and myocardial infarction in the Albany study but no such relationship existed between heavy cigarette smoking and angina. In Tables II and III, you will see similar findings in young women. During the last 15 years, I have seen 150 women, all under the age of 45 with symptoms suggestive of ischaemic heart disease; 58 of these had angina pectoris with myocardial ischaemia in their electrocardiograms and 60 had myocardial infarction. Examination of these tables indicates that women who get a myocardial infarct have different cigarette smoking habits from women who develop angina pectoris and also from women in the normal U.K. population. Various suggestions have been put forward for this difference. It is possible, although there is no good factual evidence, that cigarette smoking leads to a thrombogenic tendency. There may be a greater degree of coronary vasoconstriction, perhaps coronary spasm as described by Dr. Gorlin and as a result there may be less satisfactory formation of coronary collateral vessels in heavy cigarette smokers. A third possibility is that there are more arrhythmias in heavy cigarette smokers as a consequence of increased catecholamine and free fatty acid production; in this context, it would be interesting to try to document whether there is a higher incidence of sudden death and of immediate mortality following myocardial infarction in heavy cigarette smokers compared with non-smokers. One of the reasons for spending a little time considering cigarette smoking is that it may present a different problem so far as primary prevention is concerned when compared with the other risk factors which are perhaps more closely associated with the gradual development of coronary atherosclerosis.

There is a higher than usual incidence of angina pectoris and myocardial infarction in women whose reproductive life has ceased at an unduly early age. While a number of these women undergo premature hormonely-determined cessation of menstruation, surgery or irradiation are not uncommon causes. The removal of both ovaries, or their irradiation, can often be prevented.

Amongst the less well documented influences described in Table I, there are two which are in theory entirely preventable. One is physical inactivity and the other is rapid gain in weight. The effects of preventing physical inactivity on the development of ischaemic heart disease have not been studied and there is no current trial to determine whether increased activity has a primary protective effect. Of course, this is a very difficult subject to study. It would be necessary to identify a large group of physically inactive men and to take a randomized proportion of these men and ensure that they became physically active consistently and continuously over a long period of time. It would be equally necessary to be certain that the remaining randomized half continued to be physically inactive. I think that this is impossible to do in any culture.

It has been suggested (Heyden, 1964) that a rapid gain in weight is associated with an increase in serum triglycerides but, of course, there is no good evidence as yet that an increase in serum triglycerides alone is an adverse risk factor. One has to distinguish the increased risk which is known to occur in patients with hypercholesterolaemia from that which has yet to be shown in patients with hypertriglyceridaemia. It is also important to emphasize at this point that obesity by itself is not to be incriminated as an independent risk factor. In the Framingham and Albany surveys, obesity only becomes a significant adverse influence when it is associated with hypercholesterolaemia or hypertension. My own experience in the small group of young women already mentioned confirms this view. On the other hand, obesity has been shown to increase the work of the heart and should therefore be avoided.

**Primary Prevention Trials**

The question proposed by the title of this talk — "Is Angina Preventable?" demands consideration of the principles of primary prevention trials. Prevention of atherosclerosis itself is the most important therapeutic challenge today and it is likely to remain so until more is known about the initiating pathogenic influences. Some progress could be made, however, if preventive trials are established in groups of men who can from existing evidence be regarded as having an increased risk of developing one of the symptom complexes of atherosclerosis.

Any trial of a preventive treatment in healthy men raises certain ethical questions. Is one justified in altering the habits by drugs or by diet of
men who regard themselves as entirely healthy in the hope that they will be protected from a disease which they may not ever get? While this view commands respect and is sometimes put forward against prevention trials, many doctors feel that there is a stronger moral argument in favour of such trials. It is necessary, therefore, to examine the design of primary prevention trials.

A number of risk factors have already been defined and discussed in detail. There can be two different and independent approaches to the control of these factors. One is to control one factor at a time and the other a number of factors simultaneously. Support can be advanced for both approaches. If it is assumed that there are four different risk factors amenable to control, satisfactory control of three simultaneously might lead to a reduction for the sake of the example of 30 per cent in mortality from ischaemic heart disease. Similarly, successful control of the fourth factor alone might also lead to a reduction of 30 per cent in mortality. Since the control of several factors simultaneously might theoretically neutralize the effect of controlling some singly – for example, the increase in weight which follows the cessation of cigarette smoking – it can be postulated that control of a fourth factor might lead to an even sharper fall in the attack rate. One can conclude, therefore, that the control of several factors simultaneously and of one singly are both rational and acceptable approaches towards the implementation of primary prevention trials. Par excellence, hyperlipidaemia is the risk factor most suitable for control alone.

Control of hyperlipidaemia

There are various approaches which can be made towards the establishment of trials to control hyperlipidaemia. Perhaps the most satisfactory is to identify those individuals in the normal population with the highest risk, to randomize these and treat half of them. Another possibility is to concentrate on those who have hyperlipidaemia together with other high risk characteristics, such as a family history of vascular disease and for example, to study the effects of correcting hyperlipidaemia in the brothers and sisters of young patients with myocardial infarction. Another possibility, which is less satisfactory because it entails a mammoth trial, is to take the whole of a given population, to randomize them all and treat half of them.

For a number of years, we have been studying here in Edinburgh various means of controlling hyperlipidaemia. I have personally taken the view that any major change in the usual diet is not likely to be a practicable approach to the control of ischaemic heart disease. I do not believe even if it could be shown that a fundamental change in the normal diet reduces the attack rate from ischaemic heart disease and this has not yet been shown, that the public will pay any more attention to these findings than they are presently doing to the incontrovertible evidence that cigarette smoking is associated with lung cancer and ischaemic heart disease. Thus, we have addressed ourselves to the problem of trying to find a means of controlling hyperlipidaemia without alteration of the diet. We have studied oestrogens and thyroid hormones and rejected them both because they are only partly effective or have intolerable side effects, and during the last six years have concentrated particularly on studying and appraising the effects of Atromid-S (Symposium on Atromid, 1963).

I do not want to take up time discussing Atromid-S but there are three major points which require attention. The first is that this drug reduces elevated serum cholesterol levels and also elevated serum triglycerides (Oliver, 1962). The second is that it leads to removal of cholesterol and lipid deposits from tissues; tuberous xanthomata disappear (Borrie, 1964) and lipaemic exudates resolve in diabetics (Cullen et al., 1964). The third and perhaps the most important point is that the drug causes a large efflux of neutral sterols in the faeces (Ahrens, 1969). Thus, there is excellent circumstantial evidence that the drug not only lowers serum lipids and removes it from the tissues but that it actually promotes loss of cholesterol from the body – evidence which is lacking for diets containing polyunsaturated fats.

The Edinburgh Primary Prevention Trial

I have been so impressed by the effect of Atromid-S that two years ago I decided to take the plunge and establish a primary prevention trial using Atromid-S as a means for controlling hyperlipidaemia. This trial is jointly run by myself and Professor Morris, and with the close collaboration of Dr. R. A. Cumming from the Blood Transfusion Service. The majority of the men participating in this trial are blood donors
and all are volunteers. The age of the men is between 30 and 59 years.

The hypothesis which we are trying to test is that reduction of elevated serum lipids in healthy men leads to a decrease in the incidence of ischaemic heart disease. If after five or six years of study, we come out with a negative result, then I think this will in fact be a contribution since the air will be cleared, as it were, and presumably we can then disregard elevated serum lipid levels as a therapeutic problem. On the other hand, if the trial ends with a positive result then I believe that we may be able to say for the first time that ischaemic heart disease can really be prevented.

The aim which we have set ourselves is to show a 5 per cent reduction in morbidity and mortality from ischaemic heart disease and at a 1 per cent significance level. In order to do this, it can be calculated that 80 infarcts are required in a control group and thus 40 infarcts in a treated group. It is difficult to be exactly certain about the annual attack rate in hyperlipidaemic men in Britain but the Framingham figures probably apply and for men of the age with which we are dealing this is 1 per cent per annum. Thus, we will need to study 8,000 men in a control group for one year or better still, in view of the progression of the disease, 2,000 men over a minimum period of four years. The treated group must of course be the same size and thus the basic requirements for this study are 4,000 men and these have to be obtained from a population three times this size. This is because we are selecting hyperlipidaemic men – in other words, those above the top tertile. It is important to emphasize the magnitude of the trial and the fact that primary prevention trials cannot be undertaken with small numbers.

The design of the Edinburgh Ischaemic Heart Disease Prevention Trial is shown in Fig. 1. Olive oil is used as a placebo; it is a monoene without effect at the dosage given on serum lipid levels. As you can see, we have an additional group in our study. This is 2,000 men in a

EDINBURGH I.H.D. PRIMARY PREVENTION TRIAL

![Diagram](https://example.com/edinburgh_diagram.png)
hypolipidaemic group also receiving olive oil. This third group acts as an additional control and also allows all the team to be blind so far as the selection of men is concerned. Thus, if a man asks why he has been selected for the trial and inquires whether he has a high serum cholesterol level, we can honestly answer that we do not know since we are looking at both ends of the "cholesterol population". I should add that none of the team know which man is receiving Atromid-S or olive oil, and so we are twice blinded in this study.

At present, 1,700 men have been enrolled from the Edinburgh area. We hope to obtain 4,000 men from this area but because of the difficulty in getting these large numbers, we are shortly going to extend the trial to Prague and Budapest where the exact design of this trial will be replicated. The statistical analysis from all three centres will be made in Professor Morris' Department in London. The establishment of this trial in two other countries may be of particular value in testing the practicability of its application in the future; if similar results can be obtained from three separate cultures, then they are all the more significant and impressive.

At present, there is little to say about our own study. Obviously, there are no results available. We have been delighted with the co-operation and interest of the participants. Since it is possible to measure Atromid-S blood levels, we know that we have a very high adherence to the treatment and we also know that we have achieved the expected reduction in serum lipids.

Conclusion

I shall end by returning to the question which I set myself, "Is angina preventable?" I do not know the answer to this and I do not think that anybody else does yet. The only way, in my opinion, of finding out the answer is to establish primary prevention trials of the types which I have outlined.