Atheroma and Thrombosis
Major Threats to Our Health Today

By Paul D. White, M.D.

I HAVE accepted the challenge of speaking to this erudite society on the subject of their chief interest because of my strong conviction that I may have something of clinical importance and interest from my own experience to add to the sum of recent knowledge already established, and possibly such experience may help in the direction of further re-research, clinical and basic.

Atherosclerosis and thrombosis are two different problems unless we accept the thesis that all atherosclerosis is based on previous thrombotic processes as presented by several investigators and particularly of late by Professor Duguid. Similarly, I regard hypertension as an abnormality distinct from atherosclerosis although hypertension undoubtedly is an aggravating factor and atherosclerotic obstruction of a renal artery can cause hypertension (like Goldblatt’s clamp), while marked atherosclerotic lesions in older people can produce systolic hypertension by the establishment of a full pulse pressure due to inelasticity of the major arteries. My current belief is that the hazard is primarily secondary to the atherosclerosis itself, although I quite agree that superimposed thrombosis, blocking any one of a number of vessels such as the coronary, the internal carotid, the renal, or the iliac arteries can have very serious consequences. However, at least two thirds of the cases of sudden death encountered by Dr. Milton Helpern, with his long experience in the Coroner’s Office in New York City, showed extensive coronary atherosclerosis with no fresh thrombosis. A minority do show thrombi. In other words, one can die of angina pectoris without an actual fresh occlusion. I shall, therefore, base my remarks today primarily on the atherosclerotic lesion and its clinical significance and have less to say about the complicating or admittedly serious thrombosis that is superimposed. Nor shall I have much to say about the hemorrhages in the coronary intima or atheromatous plaques long ago described as common by Paterson of London, Ontario, and recently confirmed by Helpern and his associates in New York.

I wish to quote at the beginning of this discourse from Shakespeare and later from Lancisi. In As You Like It, Act II, Scene VII, Jaques in the forest, where a table is set, speaks as follows in answer to the Duke’s statement of

Thou seest we are not all alone unhappy:
This wide and universal theatre
Presents more woeful pageants than the scene
Wherein we play
Jaq: All the world’s a stage,
And all the men and women merely players;
They have their exits and their entrances;
And one man in his time plays many parts,
His acts being seven ages. At first the infant,
Mewling and puking in the nurse’s arms,
Then the whining school-boy, with his satchel
And shining morning face, creeping like snail
Unwillingly to school. And then the lover,
Sighing like furnace, with a woeful ballad
Made to his mistress’ eyebrow. Then a soldier,
Full of strange oaths, and bearded like the pard,
Jealous in honour, sudden and quick in quarrel,
Seeking the bubble reputation
Even in the cannon’s mouth. And then the
justice,
In fair round belly with good capon lined,
With eyes severe and beard of formal cut,
Full of wise saws and modern instances;
And so he plays his part. The sixth age shifts
Into the lean and slipper’d pantaloon,
With spectacles on nose and pouch on side,
His youthful hose, well saved, a world too wide
For his shrunk shank; and his big manly voice,
Turning again toward childish treble, pipes
and whistles in his sound. Last scene of all,
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.

In Shakespeare's day, life was short. Although we know not the actual ages in years to which he assigned these 7 periods of life, we may guess that they were short in time. The expectation of life was very limited, probably not much over 20 years, and men and women were already old at 40. In fact, 250 years after Shakespeare, which would be about 100 years ago, a woman died at 45 in a ward of the Massachusetts General Hospital and the only diagnosis on the record at that time, as I have read myself, was "old age." We know now that one does not die of old age. I myself have always found some adequate cause, such as would be noted in younger people, for example, pneumonia, severe coronary atherosclerosis, cerebral vascular accident, rupture of an abdominal aortic aneurysm, and many other events of the sort. Let me guess that Shakespeare meant that an infant or young child, that is, the first age of man, might extend from birth to the age of 5, the second period that of the whining school boy from 5 to 15, the third age that of the lover from 15 to 25, the fourth that of the soldier from 25 to 35, the fifth that of the judge, that is, an experienced professional man, from 35 to 45. Quite likely the judge in his early 40's "in fair round belly with good capon lined" had a fair amount of atherosclerosis, which may not have allowed him to survive into the sixth and seventh ages. From 45 to 55 we come to the "lean and slipper'd pantaloon," and finally at 60 second childhood. This division of years is a probability, not a certainty.

Today with the great extension of life, including not only the average expectation, which is about 70 instead of 30 as in Shakespeare's time and 40± a hundred years ago, we know that many healthy people are active in the sixties, seventies, and eighties. Rarely is pneumonia any more the old man's friend although a patient of mine, aged 107½, who was quite healthy as to his heart and cerebral condition, unfortunately did die of pneumonia, which had threatened to kill him 105 years earlier when he was an infant.

I would like to paraphrase Shakespeare's 7 ages of man by setting up my own subdivisions of life, namely 5 periods of 20 years each, which I am quite sure might well be our goal perhaps within a generation and, I certainly hope, not much later. I would divide life into 5 periods of 20 years each, the first from birth to 20, that of youth. Once upon a time this was the terrible time of life, and actors on the stage in these 2 decades died of infections right and left. Even when I was a medical student and an intern in the hospital and for a few years afterwards, the infant and childhood mortality was very high. Babies, whom I helped to take care of in 1911, died like flies, chiefly of dysentery before the pasteurization of milk. Children died of diphtheria. I myself had it but fortunately was rescued by antitoxin. Smallpox still occurred. My own father almost died of smallpox in 1881 in London and he had typhoid fever 3 times during his years of family practice. I myself escaped typhoid but it was still so current that our wards were full of it every fall. There was no room for any cardiovascular patient or anybody with cancer. Meningitis, empyema, and mastoiditis were constant emergencies and the toll was frightful. Just to think back to those days is like redreaming a nightmare. The young doctors today cannot imagine what we faced. We had a good deal of malignant endocarditis, that is, subacute bacterial endocarditis, and it was 99 per cent fatal. Tuberculosis led the list in mortality. We did not have any cholera, to be sure, although my own father's mother had died of it on Bunker Hill in Charlestown in 1860 in her very early 20's, when father was still a young infant.

Henry Christian, who was our Professor of Medicine, when I was in medical school, gave his first 6 lectures in the theory and practice of medicine on typhoid fever practically verbatim from the first chapter of Osler's textbook, the idea being that if we knew this infection we knew medicine. Today the first 6 lectures might well be given on the theory that if we know atherosclerosis we know medicine, but we certainly hope that a generation from now, this too may be in large part past history, at least in youth and middle age. The challenge is here. There is no reason why, hav-
ing accomplished what we have in the control of infections, we may not accomplish still more in the control of the current hazards to health which, by the way, include automobile accidents on the road, as well as cancer and cardiovascular disease.

I try to refer nowadays to cardiovascular disease rather than heart disease underlining the vascular part of the word and emphasizing the fact that most of our serious heart disease is not due to primary heart muscle (myocardial) disease, but rather to vascular disease. This is just as much true of cerebral diseases, diseases of the kidney and other viscera and of the legs. These troubles in major part are due to the same process, atherosclerosis, which affects the intima in all these areas of the circulation. The chief hazard in the first age period of man today (birth to 20), as I have outlined, is, so far as I know, that of accidents, with infections way down. We have not abolished them all by any means, but we have gone a long way. Accidents on the road were almost unknown when I was a medical student. It is a ridiculous state of affairs now to allow our young people to slaughter themselves on the roads.

We come now to the second 20-year period from 20 to 40. These, I call, the critical years. It is in this period of life when all seems to be going well that atherosclerosis gets going even while the candidates for trouble look so healthy, in fact too healthy, robust, with high color, and symptomless. These are the critical years for countless numbers of men in whom this process of atherosclerosis begins to be laid down. The average man in America settles down at about 25 to a life of physical indolence although with often great nervous activity in his profession or business. He has no more time to exercise or to have relaxing recreation of any sort. He has an automobile and can hardly move without it. He has a television set before which he lolls in the evening on return from his office. And his wife cooks too well. He puts on a pound or 2 or 3 of weight every year during this period; that extra weight is not muscle. When I see him as a patient at the age of 45 to 50, he is 20 to 30 pounds heavier than he was at 25. I always inquire now of my patients with coronary heart disease at the average age of 50 what their weight was at 25. It is almost invariably true that much weight has been added slowly through the years, though sometimes rapidly during the earlier years soon after marriage. Of course, it is not the actual fat under the skin to carry around that is important. This probably does not increase the burden on the heart much although it may be uncomfortable when stooping. In fact it might be good exercise to carry this weight around if there were not an infiltration into the arterial intima of much of the fat. A few ounces in the wrong places must be very much more harmful than many pounds tucked away under the skin here and there throughout the body. During these decades from 20 to 40 there are still infections to guard against, but we no longer have so much the threat of syphilis or recurrence of rheumatic fever from a streptococcus sore throat, or even appendicitis. Hypertension may start during these 2 decades, perhaps associated with the way of life and quite likely also on a hereditary basis, which is incidentally back of much of our early atherosclerosis.

Then we come to the third age of man from 40 to 60, which is the middle period of middle life where much of the disease that has been slowly building up becomes apparent by symptoms, signs, or sudden death. Hypertension, coronary atherosclerosis of high degree giving rise to angina pectoris, sudden death, or heart attacks with myocardial infarction, little strokes and big ones too, abnormalities of the circulation to the legs, and cancer are the chief threats through this period of 20 years. Here is the ripening of the hazard that started in the 20’s or 30’s. It is quite certain that the health in this period in middle age from 40 to 60 is largely dependent on what has happened before, much less in childhood, that is, before 20, than in the period from 20 to 40. It is quite obvious that we must start a campaign for "middle-aged fitness." Most of our efforts have been directed to our youth, and quite rightly, and what has been done for them has been very important. I myself belong...
to the President’s Council for Youth Fitness, but this is only a beginning. Much more important is now a campaign for middle-aged fitness, and I would like to promote this for the sake of improvement in fitness in middle age by the application of the measures about which we know a good deal already although we have not as yet all the answers.

The last 2 periods of life will also be vastly improved by this program and the male will at last have a chance to begin to catch up with the female in expected longevity. At the present time the American male expects to live only to 67 years or a bit more and the female to 73+. This difference of 6 years has increased in the last generation, largely due to the earlier hazards in middle age, chiefly atherosclerosis, which affects the male so far as the coronary arteries are concerned 24 times more often than the female under the age of 40, about 5 times more in the 40’s, and about twice more in the 50’s. We must make every effort to change the present inequality of these ages and the great surplus of widows over widowers in the middle of the later period of middle age, which I would put from 60 to 80.

Finally, we come to old age from 80 to 100, which can be much healthier if we can forestall some of the progressive changes in the intima of the coronary and other vital arteries earlier in life and if we can avoid hypertension and some of the other ills, including cancer of course, that strike middle-aged people. In addition to the prolongation of life we have the problem of maintaining health, that is, of adding life to years as well as years to life. It is in general true that the longer we can keep people living the more useful they can be. It is absurd to require retirement in the 60’s. Most people, especially in the future, will still be very useful in the 70’s and well enough to carry on quite vigorously both mentally and physically. There is no reason why a man of 70 to 80 should not continue to shovel snow if he is well, perhaps at not quite so fast a tempo. We might aim for 100 per cent mortality from coronary atherosclerosis if it kills quickly at the age of 100 during the night while the victim is asleep without any illness or incapacity prior to that time. This would mean the cancellation of the serious infections, of cancer, of accidents, of war, and many other ills. It will be a fine and perchance a final goal.

Now let me quote from a translation of Lancisi’s preface and a bit of his second volume on De Subitaneis Mortibus, that is, on sudden death, a remarkably interesting forecast of what we see and think today.

At Rome, in the summer, autumn and winter of 1705 down to the spring equinox of 1706, were many sudden deaths. The populace as they do in a Panic, invented a number of explanations: the poor quality of the tobacco; exhalations from the earth after recent earthquakes; inferior chocolate, a mysterious poison (virus) in the air. Pope Clement XI turned, as he ought, to spiritual remedies and a special liturgy, but uniting prudence and piety, appointed in January, 1706 a committee of investigation and ordered the head physician of the Medical College at Rome to have some of the bodies dissected. Lancisi was appointed head of the Commission to report to His Holiness; Cardinal Pallavicini, the Governor of Rome, gave all possible assistance and the experiments were made in a public theatre. By means of such dissections and other observations which Lancisi now publishes he arrived at certain conclusions. Meanwhile others have published dissertations in Italian and Latin, meritorious as far as they go, but these men lacked my opportunities. First, I shall deal with sudden deaths in general, a subject of late neglected, and in my second volume shall discuss whether this disease was of a universal or a particular, or, as I believe, a mixed type. I shall add some anatomic discussion. May the Reader enjoy it.

So wrote Lancisi* in the preface of his book De Subitaneis Mortibus in the year 1707, 252 years ago. He continued discussing possible causes of sudden death along this same vein in Chapter 1 of Book II:

Was the cause simple (not complicated) and universal, or particular and mixed? First, was the cause particular in individual cases? We know that in certain years or seasons, death comes to men, yes and to animals such as cattle and goats, from a pestilential condition of the air or a tainted in air or water, or from a scarcity or defect in their pasturage, and that it rages without warning. So sang Fracastoro in his golden verses:

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*Translation by Wilmer Cave Wright (unpublished—in manuscript—kindness of New York Academy of Medicine).

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Sometimes tis only beasts that are chastised,
Many or only some thereof, I do remember
One summer's baleful heat; an autumn followed
With soaking rain; the south wind blew continually,
Then every kind of goat, but of all living things
The goats alone, did perish.

But I consider it more likely that the cause of the sudden deaths at Rome was not single and absolutely common to all, but that in the majority of cases there was a special cause for each case. I conclude this from the external symptoms, and my conviction was only strengthened by experiments. For it will be shown in the following pages that the peculiar and principal cause of premature death in each case was the presence of certain seeds, which were produced gradually and were finally called into action on a sudden; as Hippocrates says: 'Diseases do not come to men suddenly but are collected and pile up little by little.' No need to blame the tobacco; since some whose nostrils were never defiled by that dust died suddenly. Or exhalations from earthquakes, since many who escaped death lived where there had been most earthquakes. Nor was the chocolate to blame, for men like Dr. Placentius, an octogenarian, or myself, accustomed to drink it as much as twice a day for 30 years either escaped altogether or had only light symptoms. On the other hand, many who never tasted it died suddenly. Nor was it a case of undetected poison in the air, for when like augurs we inspected the entrails, we found clear and well known causes for the disease.

Before the Pope ordered us to dissect, there was evidence for the theory that the cause of death was particular and not universal; in some cases there were symptoms of rupture of the blood carrying canal which had been weakened by a varix or an aneurism in the chest or abdomen. Many died of violent apoplexy due to stoppage or effusion of blood in the brain; others of a violent spasm of the heart or paralysis or obstruction of the passages of the heart and of the large arteries. Thus was hindered the passage of the blood from the heart into the lungs and the brain, and so the vital and reciprocal communication of those organs was suddenly cut off. But I must repeat again and again, that so far as I know, every one of those who died suddenly had long suffered from some disease of the fluids, the intestines, or at least of the blood vessels. . . . Therefore, to the best of my belief, these sudden deaths did not come to the healthy, but nearly always to those who had long suffered from poor health. For them this was a sort of foaming over of human nature, or an unfavorable crisis arose, with men who had long been either openly or secretly in poor health.

These remarkable observations of Lancisi were unfortunately never followed up, otherwise much more interest would have been developed in the evolution of the processes of disease that lead to sudden death, including in particular atherosclerosis, which must have been seen although it was not well described either grossly or with the help of the primitive microscopes of the day except in 1 case report in the second edition of Bonet's Sepulchretum in 1700. It is quite obvious from our experience of late years, as well as occasional notations by the more astute observers like Lancisi, that neither sudden death, nor angina pectoris, nor coronary thrombosis comes suddenly to a healthy man. The evolution of the process is a slow one, taking years at least and perhaps decades before symptoms or signs develop.

Can we, as seems quite possible, by the newer techniques of angiocardiology and other simpler methods, diagnose serious degrees of atherosclerosis at a much earlier stage than we are now able to identify them? Even if we should do so, much more would have to be done before corrective curative measures might be applied. Therefore, it seems obvious to me, and I am sure to all of you, that our chief effort in research, basic and clinical, must be directed to a more intensive study of the initial processes, physical, chemical, and hereditary in order to learn how we may counteract them. Our task is 2-fold: that of the identification of the candidate for serious trouble early in life or in middle age with a study not only of the family history but also of characteristics which we have believed to be of some importance such as body build and blood chemical findings like hyperglycemia and hypercholesteremia. Although we should attempt to make some effort to protect the whole population, nevertheless the candidates are the ones we should concentrate on first. Such candidates should be identified if possible in their early years, even perhaps in their teens, at any rate not later than their 20's. For such candidates and perhaps for all of us, simple measures may be advisable even now before we have all the proof, such measures as the avoidance of any gain in weight after

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the age of 25, the reduction of the animal fat content of our very rich American diet, and the institution of programs of regular exercise and relaxation of other sort too, with an effort to neutralize at least somewhat the emotional stress that is so characteristic of current urban life.

If we can also discover in the course of our researches, which is quite possible, magical remedies in the form of chemical substances to counteract hypercholesteremia and inherited enzyme defects, we may not need to carry out so much the other protective measures even though they seem very reasonable to us now. And while we are busy with our researches on these problems, we should try to correct the erroneous opinions and practices of countless individuals in this country who are still inclined to blame hard work as the primary cause of atherosclerosis and its complications.

Just one word about hard work. It is true that one can get very tired both physically and mentally from hard work, but I have yet to find a man or woman, otherwise healthy, who has, from hard work alone, become ill provided he or she carried out a sensible program of life avoiding the hazards that I have just mentioned.

In conclusion, may I express optimism about the future results of our researches, physical, chemical, hereditary, pathologic, and clinical on atherosclerosis, especially of the premature varieties. Within another generation, in fact I believe within a decade, with the present increasing tempo of vigorous research, we should have some definitive answers that will allow us to protect our men and to extend increasingly the expectation of a long and healthy life.

Again as I have frequently done in the past, I would like to end with another quotation from Shakespeare—"Our remedies oft in ourselves do lie, which we ascribe to Heaven."

**Summario in Interlingua**

Iste documento es le conferentia memorial Lyman Duff, presentate in 1959 a Chicago ante un reunion del Societate American pro le Studio de Arteriосclerosis. Le autor discute le thema de atheroma e thrombosis super le base de su conviction que in le composito "cardiovascular" il es le seconde parte que merita nostre prime attention. Iste attitude resulta del conviction que in le majoritate del casos de cardiopathia le morbo primari es non del toto myocardial sed plus tosto vascular e que, in plus, il es frequentemente un disordinne vascular que debe esser inermiminate primoamento quando un patiente manifesta symptomatas renal o alteremente visceral.

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**Medical Eponyms**

*By Robert W. Buck, M.D.*

In order that people may be happy in their work, these three things are needed: They must be fit for it: They must not do too much of it: And they must have a sense of success in it.—Ruskin. (Submitted by H. M. Marvin, M.D.)

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