MORBIDITY AND SURVIVORSHIP OF PATIENTS WITH EMBOLIC CHOLESTEROL CRYSTALS IN THE OCULAR FUNDUS*

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THE SIGNIFICANCE OF OBSERVED EMBOLIC CHOLESTEROL CRYSTALS IN THE ocular fundus of patients with occlusive cerebrovascular disease is well established.[1–5] This report concerns the follow-up of 208 consecutive patients with retinal cholesterol emboli and other vascular conditions, originally reported in 1966.[6] Most of the patients had one or more manifestations of vascular disease, and a significant percentage had initial complaints of amaurosis fugax, cerebral ischemia, angina, or calf claudication.

Our impression that the retinal cholesterol crystal is a warning sign of impending vascular complications in the vascular system prompted this study of the morbidity and survivorship of these 208 patients.

ANALYSIS OF DATA

We obtained follow-up morbidity and mortality data on 205 (175 males, 30 females) of the original 208 patients (178 males, 30 females). One hundred and five patients were reexamined, and information on the other 100 of the 205 was obtained by correspondence with the patient, spouse, and referring physician. The original 208 patients were seen in consecutive order and without selection.[6] Included were 34 patients seen prior to 1962, 30 seen in 1962, 37 in 1963, 49 in 1964, and 58 in 1965. The age and sex distributions are shown in Table 1. The median age of the patients when the cholesterol emboli were first observed was 64 years, with the youngest being 46 years and the oldest 84 years.

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TABLE 1. AGE AND SEX DISTRIBUTIONS OF 208 PATIENTS WITH RETINAL CHOLESTEROL EMBOLI

Age (in yrs)	No. of males	No. of females	Total
Under 50	3	0	3
50–59	56	6	62
60–69	83	15	98
70–79	34	6	40
80 or more	2	3	5
TOTAL	178	30	208

TABLE 2. CAUSES OF DEATH AMONG 135 PATIENTS WITH RETINAL CHOLESTEROL EMBOLI

Cause	No. of patients
Coronary artery disease	56
Stroke	14
"Atherosclerosis"*	14
Ruptured aortic aneurysm	11
Cancer	9
Cerebral hemorrhage	3
Unrelated	3†
Unknown	25
TOTAL	135

*Miscellaneous causes related to atherosclerotic vascular disease.
†One death each from trauma, pulmonary fibrosis, and gastrointestinal hemorrhage.

MORTALITY

As of March 1, 1972, 73 patients were alive and 135 were dead (65 per cent). The surviving patients have been followed for 6 to 15 years. Ninety-seven per cent of the patients have been followed for at least 6 years, and 70 per cent have been followed for 10 years after the observation of the embolic cholesterol crystal.

Sixteen patients died within 3 months of the observation of a retinal cholesterol embolus: 8 from coronary artery disease, and 8 from stroke, ruptured aortic aneurysm, "atherosclerosis," cerebral hemorrhage, or cancer. Of the 208 patients, 32 (15 per cent) were dead at 1 year, 61 (29 per cent) were dead at 3 years, and 112 (54 per cent) were dead 7 years after the observation of a retinal cholesterol embolus.

The causes of death of the 135 patients are listed in Table 2. Ninety-

TABLE 3. INCIDENCE OF VASCULAR DISEASE AMONG 208 PATIENTS WITH RETINAL CHOLESTEROL EMBOLI

Vascular disease	Onset in relation to when emboli were seen			
	Prior or concurrent		Subsequent	
	No.	%	No.	%
Atherosclerosis*	96	46	3	1
Angina or abnormal ECG	95	46	15	7
Carotid occlusive disease†	93	45	6	3
Stroke	80	38	33	16
Myocardial infarction	76	37	49	24
Transient cerebral ischemia	51	25	6	3
Claudication	28	13	19	9
Amaurosis fugax	24	12	3	1
Central retinal artery or branch occlusion	24	12	7	3
Cholesterol embolus in fellow eye	9	4	13	6

*Peripheral atherosclerosis obliterans, popliteal or femoral aneurysms, abdominal aortic aneurysms, renal artery occlusive disease, and others not classified elsewhere.
†As determined by angiography, decreased retinal artery pressure, or carotid bruits.

five patients died from some manifestation of atherosclerotic vascular disease. The incidence of other vascular problems (Table 3) among the dead patients, regardless of the cause of death, is not significantly different from the incidence for the total group of 208 patients or the 73 surviving patients.

Of the 56 patients who died from coronary artery disease, 40 had acute myocardial infarction as the terminal event. The 14 patients who died of "atherosclerosis" composed a miscellaneous group in which no specific terminal event was obvious, but the cause of death was considered by the attending physician elsewhere to be secondary to vascular disease. For the 11 patients who died from ruptured aortic aneurysm the incidence of large vessel atherosclerosis (peripheral atherosclerosis obliterans, popliteal, femoral, or aortic aneurysms, renal artery occlusive disease, and carotid occlusive disease) was higher than for the total group of 208 patients.

The cause of death is unknown in 25 patients. Because the morbidity resulting from vascular disease among these 25 patients is similar to that among the other 110 dead patients, we may expect that at least 17 of the 25 died from a vascular condition. Therefore, of the 135 deaths, an estimated 83 per cent are attributed to vascular disease.

MORBIDITY

We compiled the data on morbidity under ten major categories (Table 3). Each condition is reported according to its occurrence prior to, concurrent with, or subsequent to observation of an embolic cholesterol crystal in the retinal vessels.

Because of inaccuracies in some data received from the 100 patients by correspondence, this classification differs from that used in the original report.[6]

Diabetes was present in 43 patients (21 per cent) when the cholesterol embolus was observed; and subsequently 4 more patients have developed this condition. Diabetes was distributed equally among the patients in the ten major categories of morbidity, and did not appear to increase significantly the morbidity of these 43 patients. However survival was adversely affected. Thirty-four of the 43 patients (79 per cent) with diabetes have died. Six patients (14 per cent) died within 3 months, 13 (30 per cent) died within 1 year, and 22 (51 per cent) were dead within 3 years of the observation of the retinal cholesterol embolus. Because the group with diabetes is too small to assess the effect of this condition on the survival rate, the diabetics and non-diabetics were considered together in calculating the survivorship curve and the morbidity data.

The incidence of hypertension was 70 per cent for the entire group at the time the retinal cholesterol embolus was observed. Subsequently 8 additional patients developed significant hypertension.

Fifteen (7 per cent) of the 208 patients had no clinical signs, symptoms, or histories of atheromatous or arteriosclerotic vascular disease at the time the retinal cholesterol embolus was observed. Seven of these 15 patients have died: 4 from coronary artery disease, 1 from cancer, and 2 from unknown cause. Of the 7 patients who died, 1 patient had atherosclerosis obliterans with claudication, and another had carotid occlusive disease. The morbidity among the 8 surviving patients includes peripheral atherosclerosis obliterans and claudication in 2 patients and stroke in 1.

RETINAL ISCHEMIA

Retinal ischemia, manifested as amaurosis fugax, retinal infarction from occlusion of small vessels, or central retinal artery occlusion, was present in 34 patients (16 per cent) and subsequently developed in 8 additional patients (total involvement, 20 per cent). At the time the cholesterol embolus was seen, 24 patients had concurrent or prior histories of amaurosis fugax, and 3 patients subsequently developed this condition. The amaurosis fugax was invariably on the same side as the cholesterol

TABLE 4. MORBIDITY AND MORTALITY AMONG 24 PATIENTS WITH AMAUROSIS FUGAX AND RETINAL CHOLESTEROL EMBOLUS

Status and vascular disease	No. of patients
Alive	13
Dead	11
Coronary artery disease	6
Stroke	1
Ruptured aortic aneurysm	1
Atherosclerosis	1
Other	2
Concurrent and prior disease	
Carotid occlusive disease	12
Atherosclerosis	10
Transient cerebral ischemia	10
Coronary artery disease	8
Stroke	6
Retinal infarction	3
Subsequent disease	
Stroke	5
Cholesterol emboli in fellow eye	2
Transient cerebral ischemia	2

embolus. The morbidity and mortality data on these 24 patients are listed in Table 4. Eleven patients with amaurosis fugax also had strokes; in 8 of them the stroke was ipsilateral to the cholesterol embolus. The incidence of heart disease, large vessel atherosclerosis, and carotid occlusive disease among these 24 patients is similar to that for the entire group.

Twenty-four patients had concurrent or prior occlusion of the central retinal artery or its branches. Retinal infarction with ischemic edema was present in 15 of these patients, and all except 1 had carotid occlusive disease. Seven patients subsequently developed occlusion of the central retinal artery or its branches.

CEREBRAL ISCHEMIA

Cerebral ischemic phenomena, that is, strokes or transient cerebral ischemic attacks, were present in 131 patients (63 per cent) prior to or concurrent with observation of the cholesterol embolus, and 26 additional patients subsequently developed this condition. Ninety-four patients had strokes; 80 patients had an initial stroke prior to or concurrent with the observation of the embolus; and 33 patients had either their initial or an additional stroke later. Fifty-eight (62 per cent) of the 94 patients had the stroke in the cerebral hemisphere ipsilateral to the retinal cholesterol embolus. The stroke was on the contralateral side in

18 patients (19 per cent), and the stroke occurred in the vertebral-basilar arterial system in 12 patients (13 per cent). The location of the cerebral infarct in 6 cases is unknown. Sixty-three (67 per cent) of the 94 patients with strokes have died. The incidence of the various other manifestations of vascular disease among those patients with strokes, either prior, concurrent, or subsequent, and the causes of death among the 63 patients with strokes are not significantly different from the incidence for all 208 patients.

CORONARY ARTERY DISEASE

Coronary artery disease (myocardial infarctions, angina, or an abnormal electrocardiogram) was present in 125 patients (60 per cent) concurrent with the cholesterol embolus, and subsequent heart disease developed in 14 additional patients. Interestingly, 15 patients later developed angina or an abnormal electrocardiogram, and 49 patients (24 per cent) had subsequent myocardial infarctions.

ATHEROSCLEROSIS

Large-vessel atherosclerosis (peripheral atherosclerosis obliterans, popliteal or femoral aneurysms, abdominal aortic aneurysms, renal artery occlusive disease, carotid occlusive disease, and lower extremity claudication) was present in 146 patients (70 per cent) at the time the cholesterol embolus was observed, and these conditions subsequently developed in 11 additional patients. The numbers of patients with concurrent and subsequent atherosclerosis of the aortico-iliac vessels, carotid occlusive disease, and claudication are listed separately in Table 3.

Altogether 193 patients (93 per cent) had some manifestation of vascular disease when first seen, and 7 additional patients subsequently developed a vascular problem. Multisystem involvement from vascular disease was present in 71 per cent of the patients.

The heterogeneity of vascular involvement is illustrated by the data which show that 131 patients had cerebral ischemia, 125 patients had coronary artery disease, and 146 patients had atherosclerosis involving various large arteries. However in 40 patients the manifestations were not heterogeneous and involved essentially only one organ system (Table 5).

Nine patients had no systemic manifestations other than cerebral ischemia, that is, stroke or transient cerebral ischemic attack. At the time the cholesterol embolus was observed, 6 patients had old or recent strokes and 5 patients had transient ischemic attacks. Four of the 9

TABLE 5. VARIETIES OF ATHEROSCLEROTIC INVOLVEMENT AMONG 208 PATIENTS WITH RETINAL CHOLESTEROL EMBOLI

Vascular disease at time of observation of the cholesterol embolus	No. of patients with isolated manifestation	Total no. of patients with manifestation
Cerebral ischemia*	9	131
Atherosclerosis†	15	146
Coronary artery disease‡	16	125
No evidence of vascular disease	15	

*Strokes, transient attacks of cerebral ischemia.
†Peripheral atherosclerosis obliterans, popliteal, femoral, or aortic aneurysms, renal artery occlusive disease, carotid occlusive disease, and other conditions not classified, but related to atherosclerotic vascular disease.
‡Myocardial infarction, angina, abnormal electrocardiogram.

patients are dead: 1 died from a stroke, 2 from cerebral hemorrhage (one of these was on long-term anticoagulant therapy), and 1 from heart disease. Of the other 5, 1 subsequently had a stroke, 3 developed coronary artery disease, and 1 developed carotid arterial stenosis.

Of the 15 patients with only peripheral atherosclerosis and retinal cholesterol emboli, 11 have died. Five died from coronary artery disease, 2 from ruptured abdominal aneurysm, 1 from stroke, 1 from cancer, and 2 from unknown cause.

Only 16 patients (15 males) had isolated coronary artery disease. Six patients currently survive. At least 7 patients died from coronary artery disease, 1 from cancer, and 2 from unknown cause. Five patients developed cerebral ischemia, and 1 had amaurosis fugax.

The survivorship curve for the 208 patients is illustrated in Figure 1, and the actuarial data are listed in Table 6. The survivorship curve is based on the actuarial method.[7,8] The survivorship curve for the 193 patients with symptomatic vascular disease when first seen and that for the total group of 208 patients are similar. The inclusion of the mortality data from the 15 patients who had no other evidence of vascular disease with the data from the 193 symptomatic patients did not alter the observed survival rate. The observed survival rate for the patients with cholesterol emboli (and other vascular problems) is markedly less than that expected for a group of the same age and sex (Minnesota Life Table for white population).

COMMENT

The high incidence of atherosclerotic vascular disease among the 208 patients in our series is not unexpected, since this association has been previously reported. Furthermore the relationship of cholesterol emboli

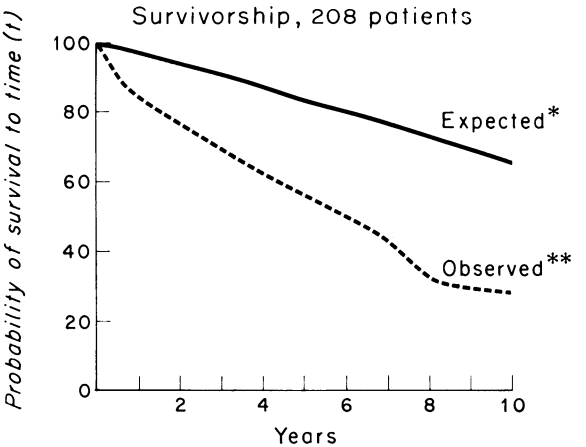

FIGURE 1

Observed (**) survivorship curve for 208 patients with embolic cholesterol crystals in ocular fundus. Expected (*) survivorship curve for same age and sex distribution. Minnesota white population, 1950 Life Table.

TABLE 6. ACTUARIAL ESTIMATION OF SURVIVAL

Time interval after diagnosis	Alive and under observation at beginning of interval	Deaths in interval	Withdrawals alive in interval	Survivorship $P(t)$
0–3 mos	208	16	4	1.000
3 mos	188	8	0	0.922
6 mos	180	6	0	0.883
9 mos	174	2	0	0.853
1 yr	172	15	1	0.844
2 yrs	156	14	0	0.770
3 yrs	142	15	1	0.701
4 yrs	126	13	0	0.626
5 yrs	113	10	1	0.562
6 yrs	102	13	22	0.512
7 yrs	67	15	19	0.438
8 yrs	33	2	8	0.321
9 yrs	23	1	6	0.299
10 yrs	16	1	3	0.284
11–15 yrs	12	4	8	0.264
	TOTAL	135	73	

to atheromatous cerebrovascular disease and the close correlation between the appearance of the cholesterol crystal and the cerebral ischemic episode (ipsilateral to the emboli in 80 per cent) were discussed in the initial report of these patients.[6] Likewise the origin of these crystals from ulcerating atheromatous plaques in the lumina of large vessels whose circulation goes to the head and the similar origin of atheromatous particles, large and small, which can produce irreversible oculocerebral infarction have been discussed previously.[6]

The incidence of various manifestations of vascular disease both prior to and concurrent with the observation of the cholesterol embolus, although categorized differently here than in the initial report, remains essentially the same. Subsequent events in these patients consisted mostly of myocardial infarctions, strokes, and ocular ischemia. Thirteen patients later had embolic cholesterol crystals in the opposite eye. The incidence of recorded subsequent events is a minimal figure in spite of the 6-year follow-up of 97 per cent of the patients, because many died unattended by a physician or the final diagnosis was not accurately established.

The survivorship curve for the 208 patients is derived from a heterogeneous population of patients with different manifestations of atheromatous vascular disease, because most of the patients (71 per cent) had multisystem involvement. Since so few patients had isolated involvement, for example, cerebral ischemia (9 patients), coronary artery disease (16 patients), or large vessel atherosclerosis (15 patients), we could not estimate survivorship separately for these subgroups. Furthermore survivorship depends on many other factors, such as hypertension, smoking, and diabetes, which are not considered here. Our heterogeneous group with the cholesterol emboli are compared, therefore, with the general population of the same age and sex distribution.

During the first year the patients with the cholesterol emboli have an observed survival rate that was 13 per cent less than expected. The difference was 27 per cent less by the fifth year, and 40 per cent less by the eighth year, after observation of the retinal cholesterol embolus. Whether these data apply to patients who have only the embolus but no other signs or history of vascular disease is unknown. However the inclusion of the 15 patients without evidence of atherosclerosis along with the 193 patients who had evidence of atherosclerotic vascular disease did not improve the survival rate.

Whether an embolic cholesterol crystal in the ocular fundus is a decided risk factor in the survival of these patients, or whether it is the high incidence of other manifestations of vascular disease that pre-

disposes them to so many subsequent vascular complications, cannot be definitely stated at this time. Further follow-up of patients who have retinal cholesterol emboli but no other evidence of vascular disease will be helpful in demonstrating our impression that the embolic cholesterol crystal is a warning sign of a future disaster in the vascular system.

SUMMARY

A study of the morbidity and survivorship of 208 consecutive patients with embolic cholesterol crystals in the retinal vessels revealed that these emboli are closely associated with systemic manifestations of atherosclerosis and indicate ulceration in an atheromatous plaque; the ages of the patients ranged from 46 to 84 years, and almost all (97 per cent) were followed for at least 6 years. The observation of this embolic crystal in the ocular fundus should lead the clinician to a full investigation of the patient's vascular status.

ACKNOWLEDGMENT

Dr Lila R. Elveback prepared and analyzed the actuarial data.

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DISCUSSION

DR G.N. WISE. I appreciate very much the authors permitting me to see their manuscript well before this meeting.

They are to be congratulated on an excellent statistical report which signifies the importance of cholesterol emboli as a sign of generalized arteriosclerotic vascular disease. The increased morbidity and mortality in these patients were expected, but the incidence of the various arteries attacked was

surprising. The number of patients having amaurosis fugax, and especially those having carotid artery occlusion, was much lower than I would have anticipated. Do the authors believe that all carotid occlusions were diagnosed? There are both asymptomatic carotid occlusions and those which, because of collateral circulation, do not show significant abnormality of their central retinal artery pressures. I was also surprised at the relatively high incidence of ruptured aortic aneurysms and the fact that coronary artery disease accounted for so many more deaths than stroke.

In view of the authors' great experience in this area, I would like to ask several related questions:

1 Have they ever seen a retinal artery obstruction of any size due to cholesterol crystals alone?
2 Have they ever observed a platelet embolus and, if so, did it lead to transient (amaurosis fugax) or permanent retinal artery obstruction?
3 What type of investigation do they recommend for patients having cholesterol emboli in retinal arteries; that is, how far do they proceed in their investigation, and what are their criteria for recommending carotid angiography?

Dr J. Reimer Wolter. It is a pity that in this excellent study the authors have chosen the term "cholesterol crystal emboli" to describe the emboli seen with the ophthalmoscope in retinal arterioles of their patients, and I think they have no good basis to state that these emboli were isolated cholesterol crystals.

General and ophthalmic pathologists know that retinal emboli of this type are parts of atheromas located in larger arteries up-stream. The firm parts that break off these atheromas are composed of amorphous lipid and calcified materials, fibrosis, foreign body reaction, and cholesterol crystals. The cholesterol crystals may be the only component of the emboli that is visible with the ophthalmoscope, but pathological experience has shown that the other substances are usually also present. I would like to suggest that we call these emboli "atheromatous emboli" unless we have definite proof that we are dealing with pure cholesterol crystals.

Mr Stephen Miller. I have been interested in this subject since reading Dr Hollenhorst's original paper about cholesterol emboli. At the moment we are following up a smaller series of patients who have presented an embolus but no other signs. Unfortunately this study began only three years ago and it isn't possible to give you any figures, but there are two points in the paper that I would like to ask the authors about.

Was there any correlation between the death rate and blood pressure? Was it related in any way?

Second, we all know that the abdominal aorta is much more open to atheroma in the aortic arch, and I wonder if these dissecting aneurysms which the authors have described affected the abdominal aorta or whether they affected the aortic arch or the thoracic aorta.

May I say just one more thing, Mr President. It has been a great privilege for me to be your guest. It is an honor which I shall long cherish, and I would like you and your officers and members to realize how much I have enjoyed this meeting.

DR HOLLENHORST. I very much appreciate the stimulating discussion by Dr Wise, Dr Wolter, and Mr Miller. Although we have clearly shown that patients with cholesterol emboli in the retina have a significantly lower survival rate than do members of the general population matched for age and sex on the actuarial tables, we have not shown that the embolizing patients have a higher morbidity or mortality than do atherosclerotic patients without evidences of embolization.

Because atherosclerosis is a widespread heterosystemic condition which may involve a variety of sites in the body, there are no actuarial tables at all for this disease which one may use in comparison with our cases.

In response to Dr Wise's questions, I can answer each of them only briefly. First of all, the reason why so low a figure of amaurosis fugax is encountered in this series: Most of the time I think we assume that about 40 per cent of the patients with transient ischemic attacks suffer also from amaurosis fugax, but in our study the incidence was much lower than that, and the reason is that not all of these patients embolize from stenotic carotid arteries. They were all unselected, consecutive cases. Every embolus that I saw was included in the series, regardless of the reason for referral. Not all examples of carotid stenosis were diagnosed, only in general those with symptomatic or physical signs pointing toward the carotid arteries other than the cholesterol crystal.

The high incidence of death from coronary artery disease is not at all surprising. This was true also in the large Mayo Clinic study of stroke patients. The majority of those also died of coronary artery disease.

We have seen only a few obstructions of an artery by cholesterol crystals alone. These were invariably very small vessels. However we have encountered several patients whom we examined shortly after an attack of amaurosis fugax, in which the bolus of crystals apparently lodged initially at the cribiform plate, and when we examined the retina there were numerous crystals scattered about which later disappeared. I remember one lady was very conscious of her carotid artery. Every time she palpated it she had a shower of emboli into the retina.

Most occlusions in the retinal arterioles result from fibrin, platelet, or other debris which Dr Wolter, I am sure, has properly referred to as atheromatous emboli, and usually there may be non-obstructing cholesterol crystals in the same arterioles or in other sites in the same eye which do not obstruct the vessel. Commonly when one sees one of these soft white emboli which mold up into the retinal circulation in patients with atheromatous disease, quite often there may be cholesterol crystals distally in the same vessel which obviously arrived there before the obstructing embolus did.

I still insist that one can tell cholesterol emboli from atheromatous emboli

or other material, in that all of these crystals, as one sees them in the retina, have an angular form. One can also see little pieces, rhomboid in shape, breaking loose, and in the first embolus shown on the screen one could see one of those which broke off while under my observation. Also, there have been a number of studies of the retina, particularly Noble David's in Miami, which showed that these were cholesterol crystals. There have also been two other reports which I can't quote at the moment, which showed this very definitely.

Quite often when one sees one of these soft emboli which do the obstructing, one can actually see brightly glinting material inside of these emboli, which I assume (although I have no proof for it) are probably crystals that are encompassed within the white molding emboli or fibrin-platelet type of embolus. So I am eagerly awaiting further studies by someone else. We have not been very successful in getting any of these patients to examine post mortem.

In answer to Dr Wise's question, our procedure when we see a cholesterol embolus consists of the following four things: First, further thorough ophthalmoscopy, looking for as many of these as we can see, including observation of very small branches as we are doing ophthalmodynamometry, because this often brings other crystals into view. Second, measurement of the retinal artery pressures. Third, auscultation of the carotid arteries to just beneath the angle of the mandible as far up as one can reach. Fourth, palpation of the carotid pulse. This is followed by a complete general examination with attention to other evidences of atherosclerosis. If one finds other evidences of atherosclerosis, then the patient is referred for consideration of endarterectomy.

We do angiography on patients with carotid stenosis only after such thorough examination and consultation with the vascular neurologist group. We do angiography only on patients who have not had a cerebral infarct, and only on patients who are having symptoms – that is, ischemic attacks or amaurosis fugax, and who, we are reasonably certain, are prime candidates for carotid endarterectomy.

We do not do angiograms merely to satisfy our curiosity about the status of the carotid arteries, because it is well known that one carotid artery can have a completely silent occlusion and that this seems to do the patient no harm at all until the other carotid becomes involved.

In answer to Mr Miller's questions about the abdominal aorta being involved, these aortic aneurysms occupy all parts of the aorta. Some were in the ascending aorta and some in the arch, and some were in the abdominal part of the aorta. It is a very surprising finding. This was already noted in my original paper, since 24 out of the 208 patients who came in, and whom I saw without knowing they had any aortic aneurysm, had this aneurysm at the time we first noted the cholesterol crystal embolus.

Thank you very much.