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Quantitative Extent of Atherosclerotic Plaque in the Major Epicardial Coronary Arteries in Patients with Fatal Coronary Heart Disease, in Coronary Endarterectomy Specimens in Patients with Non-Fatal Coronary Artery Disease, in Aorta-Coronary Saphenous Venous Conduits, and Means to Prevent the Plaques: A Review After Studying the Coronary Arteries for 50 Years

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Abstract

This review tries to answer the following 15 questions: Is atherosclerosis a systemic or a regional disease? Is atherosclerosis in any particular region focal or diffuse? What is the quantity of atherosclerotic plaques in endarterectomy specimens of the right coronary artery in patients undergoing coronary artery bypass grafting (CABG) compared to that in the right coronary artery in patients with fatal coronary artery disease? How do the units used for measuring arterial narrowing by angiography compare to the units used for measuring arterial narrowing at necropsy? What do atherosclerotic plaques consist of in coronary arteries in patients with fatal coronary disease? What is the quantity of atherosclerotic plaque in bypassed -vs- non-bypassed native coronary arteries in patients dying early (<60 days) or late (>60 days) after coronary artery bypass grafting? What is the frequency of acute coronary lesions and multi-luminal channels at necropsy in patients with unstable angina pectoris, sudden coronary death, and acute myocardial infarction? What is the mechanism of luminal widening by angioplasty in the coronary arteries? What observations suggest that atherosclerotic plaques are the result at least in part of organization of thrombi? Is atherosclerosis a multifactoral or a unifactoral disease? What characteristics distinguish carnivores and herbivores? What are reasonable guidelines for whom to treat with lipid-altering agents? What is the rule of 5 and the rule of 7 in statin therapy? What is the effect of lipid lowering drug therapy on coronary luminal narrowing? What are some requisites for a healthy life?

Key Words: Coronary artery disease; coronary bypass grafting; low-density lipoprotein cholesterol.

Abbreviations: AMI=acute myocardial infarction, CABG=coronary artery bypass grafting, CAD=coronary artery disease, LDL=low-density lipoprotein, RCA=right coronary artery.

Introduction

Most studies describing the severity of coronary artery disease (CAD) refer to it as one, two, or three vessel diseases or "left main disease." That classification usually designates the number of major (right, left main, left anterior descending, and left circumflex) epicardial coronary arteries narrowed to a certain degree, often 70% diameter reduction, by angiogram or >75% cross-sectional narrowing by intra-arterial ultrasonic imaging or when studied at necropsy. This type of classification obviously has proven to be useful from both therapeutic and prognostic standpoints. This classification, however, does not describe the extent of the narrowing or the extent (quantity, burden) of the atherosclerotic plaques in the full lengths of each of the 4 major epicardial coronary arteries. This review summarizes a number of studies describing the amounts of luminal narrowing not at a single point in any of these 4 coronary arteries but in each 5-mm segment of each of the 4 major epicardial coronary arteries in a large number of patients with fatal CAD studied at necropsy or in those with non-fatal CAD who had coronary endarterectomy specimens available for study. Since the lengths of the 4 major epicardial coronary arteries in adults generally add up to about 27 cm (right = 10; left main = 2; left anterior descending = 10; left circumflex [quite variable] = 6), a total of about 54 five-mm segments of coronary artery are generally available for examination in each patient (Figure 1). One histologic section of each 5-mm segment was stained for elastic tissue (so that the internal elastic membranes would clearly be discernable for baseline demarcation purposes), usually a Movat stain, and examined from each patient. Before cutting the 5-mm long segments, each major epicardial coronary artery was carefully excised from the heart and decalcified, if necessary. This method is both time consuming and expensive, and both reasons probably account for the absence of this type study by nearly all investigators. The studies described herein were carried out over several decades and with few exceptions before statin therapy was

available. I like to refer to this 5-mm segment approach as a *quantitative* one and the 1-, 2-, 3-vessel disease approach as a *qualitative* one.

Is atherosclerosis a systemic or a regional disease?

A systemic disease. A high percentage of patients with claudication, abdominal aortic aneurysm or obstruction, and carotid arterial narrowing die from atherosclerotic CAD. Mautner and associates (1) reported at necropsy the status of each 5-mm long segment of each of the 4 major coronary arteries in patients with an abdominal aortic aneurysm ≥5.0 cm in its widest transverse diameter. During life, 12 of the 27 patients (44%) had symptoms of myocardial ischemia and 10 (37%) died from its consequences. Grossly visible left ventricular foci of necrosis or fibrosis, or both, was present in 15 patients (56%). Of the 27 patients, 23 (85%) at necropsy had narrowing 76% to 100% in cross-sectional area of ≥1 major coronary artery by atherosclerotic plaque. Of the 1,475 five-mm segments of the major coronary arteries in the 27 patients, 17% were narrowed 0 to 25% in cross-sectional area; 37%, 26% to 50%; 28%, 51% to 75%; 15%, 76% to 95%, and 3%, 96% to 100%. The percentages of these 5-mm segments narrowed >75% in cross-sectional areas were similar in the right, left anterior descending, and left circumflex coronary arteries. The authors concluded that patients with abdominal aortic aneurysm nearly always have diffuse and severe coronary atherosclerosis.

Mautner et al (2) also determined the amounts of coronary arterial narrowing by atherosclerotic plaque at necropsy in patients who had had lower extremity amputation secondary to peripheral arterial atherosclerosis. During life, 15 of the 26 patients (58%) had symptoms of myocardial ischemia and 12 of the 26 (42%) died from it. Grossly visible foci of left ventricular necrosis or fibrosis, or both, was present in 21 patients (81%), and 24 (92%) of the 26 patients had narrowing 76 to 100% in cross-sectional area of ≥1 major epicardial coronary

arteries by atherosclerotic plaque (mean 2.3± 1.0/4.0). Of the 104 major coronary arteries in the 26 patients (4 per patient), 60 (58%) were narrowed >75% in cross-sectional area by plaque. The 4 major coronary arteries were divided into 5-mm segments and the mean percentages of the resulting 1,322 segments narrowed in cross-sectional area were the following: 17%, 0 to 25%; 20%, 26 to 50%; 35%, 51 to 75%; 19%, 76 to 95%, and 9%, >95%. The percentages of the segments narrowed >75% in cross-sectional area were similar in the right, left anterior descending and left circumflex coronary arteries. Thus, patients with peripheral arterial atherosclerosis severe enough to warrant amputation nearly always have diffuse and severe coronary atherosclerosis at the time of necropsy.

Is atherosclerosis in any specific region focal or diffuse? A look at the coronary arteries.

Table 1 shows the modes of death in fatal CAD in 1,889 patients' ≥30 years of age studied at necropsy by Roberts and colleagues (3) from 1960 to 1990. Table 2 shows the various coronary events in a number of patients studied at necropsy in which each 5-mm segment of the 4 major coronary arteries was studied histologically (4-34). Several of these studies were summarized by Roberts in 1989 (35). A summary of the findings in one group, namely acute myocardial infarction (AMI), is summarized in figures 2 and 3 (8). The 4 major coronary arteries in all of these coronary subsets were excised intact from the heart, decalcified (if necessary) and divided into 5-mm segments and a histologic section was prepared from each and stained by an elastic tissue stain (Movat) and then examined histologically. The average number of 5-mm segments per patient was 55. Of the patients with AMI studied at autopsy, 34% of the 5-mm segments of the 4 major coronary arteries were narrowed 76 to 100% by atherosclerotic plaque alone (excludes thrombus); 38% were narrowed 51 to 75%; 23%, 26 to 50%, and 5%, 0 to 25%, and not a single segment was devoid of plaque (Figure 2). The quantity of narrowing, and

this was typical of all the coronary subsets studied, in each of the 4 major coronary arteries was similar (Figure 3). In the 27 patients, 1,403 five-mm segments were examined. The amounts of narrowing at each of the 4 categories of narrowing in the right, left anterior descending, and left circumflex were similar. The percent of patients with severe narrowing (76 to 100%) of the left main coronary artery was approximately 10%.

The quantity of myocardial scar in patients with a healed AMI is not proportional to the quantity of plaque in the coronary arteries. No differences in the quantity of coronary plaque was observed in patients with large healed -vs- small healed infarcts (Figure 4).

The quantity of coronary plaque was found to be greater in patients with unstable angina pectoris than in any other coronary subsets (Figure 5) (5). Although the left ventricular ejection fractions were normal in each patient, nearly half of the 5-mm coronary segments were narrowed >75% in cross-sectioned area by atherosclerotic plaque alone. A montage of photomicrographs from the 5-mm cross sections in one of these patients is shown in figure 6. No segment was devoid of atherosclerotic plaque.

The coronary arteries are not the only arterial system in which the atherosclerotic process is diffuse in patients with symptomatic or fatal atherosclerotic events. Vascular surgeons have observed that the atherosclerotic process in the legs is diffuse in patients with femoral arterial occlusive disease (36). Shown in figure 7 are endarterectomy specimens of superficial femoral arteries from 3 patients. The entire endarterectomy specimen in each patient is >15 cm in length. The lumen of each artery was filled with plaque. There were no normal areas, i.e., areas devoid of plaque.

What is the quantity of atherosclerotic plaque in endarterectomy specimens of the right coronary artery in patients undergoing coronary artery bypass grafting (CABG) compared to that in the right coronary artery in patients with fatal coronary artery disease?

Roberts and colleagues (37) compared the amounts of cross-sectional area narrowing of

the right coronary artery (RCA) in patients having endarterectomy of this artery at the time of CABG (live patients) to the amounts of narrowing of the same artery at necropsy in patients with fatal CAD (Figure 8). They examined each 5-mm segment of endarterectomy specimens of the RCA in 39 patients having this procedure at the time of CABG and compared findings in them to the amounts of narrowing of each 5-mm segment of RCA in 141 patients with fatal CAD studied at necropsy. Of the 564 five mm RCA segments in the endarterectomy specimens, 371 (66%) were narrowed >75% in cross-sectional area by atherosclerotic plaque: another 112 (20%), 51 to 75%; 64 (11%) 26 to 50%; and 17 (3%) 1 to 25%. In contrast, of the 2,699 five-mm segments of the RCA in the 141 necropsy patients with fatal CAD, 1,217 (45%) were narrowed >75% in cross-sectional area; another 966 (36%), 51 to 75%; 405 (15%), 26 to 50%, and 114 (4%), 1 to 25% by plaque. These authors concluded that the amount of severe narrowing found in coronary endarterectomy specimens excised at the time of CABG in live patients is at least as great as that found using the same technique in patients with fatal CAD studied at necropsy. The event which prompted the CABG in many of these patients was their first event. This observation suggests that an even greater emphasis should be placed on primary prevention of atherosclerotic events and, indeed, of atherosclerotic plaques. A more recent study (38) confirmed these observations and described the frequency of coronary endarterectomy at the time of coronary bypass by several different cardiac surgeons. Some cardiac surgeons frequently perform coronary endarterectomy and others rarely at the time of CABG.

An endarterectomy specimen (a continuous plaque) of the RCA is shown in figure 8. ("Endarterectomy" is a misnomer because the "endarterectomy" specimen virtually always also includes a portion of media. The split is in the media, not at the junction of intima and media such that the internal elastic membrane is incorporated into the endarterectomy specimen.)

How do the units used for measuring arterial narrowing by angiography compare to the units used for measuring arterial narrowing at necropsy?

The unit of measurement of angiography is *diameter reduction*: the area of maximal narrowing is compared to an adjacent area which is assumed to be normal such that if the narrowed area is half that of the adjacent area it is considered a "50% lesion" (Figure 9 and 10) (39). *Cross-sectional area* narrowing is the unit used at necropsy and by echocardiography. The circle is divided into 4 quadrants, and the severity of narrowing is determined by how many of these quadrants are obliterated by plaque. In general, a 75% cross-sectional area narrowing is equivalent to a 50% diameter reduction. Also, in general, an artery (or valve orifice) has to be narrowed >75% in cross-sectional area for flow to be diminished. If the 4 major epicardial coronary arteries have diffuse plaque in them (as in patients with symptomatic or fatal CAD) there is no area in the artery that is completely normal. Thus, an area of maximal narrowing is simply compared to an adjacent area which is assumed to be normal but in actuality is simply less narrowed (Figure 10). There is a built-in under-reading by coronary angiography because of the absence of totally normal segments to compare to the narrowed segments. Intra-luminal echocardiography, in contrast to angiography, compares quite favorably to cross-sectional area examination of endarterectomy or necropsy specimens because it too uses cross-sectional area narrowing as the unit of measurement.

Shown in figure 11 is an angiogram of a RCA in a patient with unstable angina pectoris who was scheduled for coronary bypass because of severe narrowing of the left anterior descending and the left circumflex coronary systems. The judgment was made that, although there was a bit of irregularity of this RCA, it did not need the insertion of a conduit. Figure 12, however, shows photomicrographs of each 5-mm segments of that RCA because the patient died 3 days after CABG and was studied at necropsy. Every 5-mm segment contains plaque. The

purpose of these photomicrographs is not to suggest that the clinical judgment was wrong but simply to demonstrate that each of the 5-mm segments contained plaque. Many of the lumens stretched from one side of the artery to the other and that is why the angiogram appeared to be relatively devoid of significant narrowing. Angiograms, of course, are luminograms and they do not demonstrate the quantity of underlying atherosclerotic plaques. The amount of narrowing shown by angiography is the tip of the iceberg; most of the iceberg (plaque) is below the surface of the water (Figure 13).

What do atherosclerotic plaques consist of in coronary arteries of patients with fatal coronary disease?

There appears to be a general belief that coronary atherosclerotic plaques consist mainly of lipids, but multiple studies of all 5-mm segments of the 4 major coronary arteries in a variety of patients show that fibrous tissue in the dominant component of coronary plaques (30, 40-45), including the young as well as the old (31, 32), those with extremely high serum cholesterol levels (homozygous familial hypercholesterolemia) (30), inflammatory coronary disease - Buerger's disease (45), and cocaine addicts (27). Of the various components of coronary atherosclerotic plaques in patients with fatal coronary events, irrespective of the amounts of luminal narrowing, *fibrous tissue* is the dominant component, be it dense or be it cellular (Figure 14). In the segments that are minimally narrowed (1 to 25%) cellular fibrous tissue still is the dominant component whereas in those segments causing luminal narrowing 96 to 100% in cross-sectional area, dense fibrous tissue is the dominant component. *Calcium* occurred only in those segments narrowed >50% in cross-sectional area and progressively increased as the quantity of narrowing increased. *Foam cells* are rare in severely narrowed coronary segments.

Fibrous tissue appears to be is the dominant component of coronary plaques in both the young and the old (31, 32). The various components of coronary plaques in a group of patients

with *juvenile diabetes mellitus* is shown in figure 15 (43, 45). The average age of onset was 9 years, and the average age of death was 29. Shown in the figure are the combined findings in the patients. In the 5-mm segments narrowed 1 to 25%, cellular fibrous tissue was the dominant component whereas in the segments narrowed 96 to 100% dense fibrous tissue was the dominant component. Calcific deposits were infrequent. The quantity of extracellular lipid was relatively small. Fibrous tissue appears to be the dominant component of plaques of both young and old people.

The composition of plaques in saphenous vein conduits is similar to that of the *native coronary arteries* after a period of several years as shown in figure 16 (41, 42). Cellular fibrous tissue was the dominant component in the 5-mm segments of the saphenous vein grafts that were minimally narrowed (1 to 25%) and dense fibrous tissue was the dominant component in the grafts which were narrowed 96 to 100% in cross-sectional area. In the native coronary arteries, irrespective of the degrees of luminal narrowing, dense fibrous tissue was the dominant component. Cellular fibrous tissue was the next most frequent component. The composition of plaque in 'native' coronary arteries and in saphenous venous grafts varies a bit among men -vs- women as shown in figure 17 (43).

What is the quantity of atherosclerotic plaque in bypassed -vs- non-bypassed native coronary arteries in patients dying early (<60 days) or late (>60 days) after coronary artery bypass grafting?

If CAD is so diffuse, as described in earlier portions of this review, is it logical to put conduits in some native arteries and no conduits in others? This question was examined by Waller and Roberts (10) who compared the quantity of narrowing in the native coronary arteries that were bypassed versus those not bypassed in patients dying early (<60 days) and later after CABG (Figure 18). The percent of the 5-mm segments narrowed >75% in cross-sectional areas was similar in the bypassed and non-bypassed native coronary arteries whether the patient died

early or late (Figure 19). This is another example of the diffuseness of coronary atherosclerotic plaques in patients with symptomatic CAD.

What is the frequency of acute coronary lesions and multi-luminal channels at necropsy in patients with unstable angina pectoris, sudden coronary death, and acute myocardial infarction?

Kragel and colleagues (33) examined this question by studying 5-mm sections of each of the 4 major coronary arteries in a group of patients who had a single isolated coronary event (Table 3). They studied 14 patients at necropsy with *unstable angina pectoris* and these individuals had no foci of left ventricular necrosis or fibrosis, indicating that they never had either an acute or healed myocardial infarct and none of them died suddenly. They studied another 21 patients who *died suddenly outside the hospital* and these individuals likewise had never had either an acute or healed myocardial infarct and their records indicated that angina pectoris was absent. They also studied 32 patients who had had a *fatal first AMI*. The authors knew that it was their first and only coronary event because there were no scars in the left ventricular wall. These patients died in the hospital and they did not at any time have angina pectoris. Thrombi were present in a coronary artery in some patients in all 3 groups, but their frequency and size varied enormously: thrombi occurred in 73% of the AMI patients and it completely occupied the lumen overlying an atherosclerotic plaque. Nearly 30% of those with unstable angina pectoris and sudden coronary death had thrombi but these were minute (<10% of the residual lumen), located over a plaque, and they did not interfere with blood flow. *Plaque rupture* occurred predominately in the patients with acute infarcts but it was not universal in that 25% of these patients did not have evidence of ruptured plaque even though every 5-mm sections of the 4 major epicardial coronary arteries were studied histologically. *Plaque hemorrhage* was seen far more frequently in the AMI group but the hemorrhage did not appear to further narrow the lumen of the coronary artery at the site of the hemorrhage. *Multi-luminal channels* occurred

in one or more 5-mm segments in all patients, most prominent in the patients with unstable angina pectoris.

Brosius and Roberts (46) described among patients with their first AMI the amount of narrowing at the site of the thrombus due to underlying atherosclerotic plaque versus the amount by overlying thrombus. They found that at the site of the thrombus the lumen was narrowed in cross-sectional area by underlying plaque from 33 to 98% (mean 81%), indicating that the amount of lumen occupied by thrombus varied from 67% to 2% (mean 19%). This finding supports the observation that primary angioplasty produces better results early after AMI than does thrombolysis: the latter simply lysis the clot whereas angioplasty both disrupts the clot and cracks the underlying plaque resulting in a wider lumen. Just proximal and just distal to the thrombus, the amount of lumen occupied by plaque averaged 76% proximally and 81% distally.

What is the mechanism of luminal widening by angioplasty in the coronary arteries?

Potkin and Roberts (23) examined 5-mm segments of the 4 major epicardial coronary arteries in patients who had undergone coronary angioplasty and found that the mechanism by which the procedure works is by cracking the underlying atherosclerotic plaque. It is not by compressing the plaque. Figure 20 shows a gross photograph with partial cracking of the plaque and a small dissection. Figures 21 and 22 show photomicrographs of plaques cracked by angioplasty with dissection of a portion of the coronary media in several. Both mechanisms serve to widen the lumen. Figure 23 shows what may happen late after coronary angioplasty: cellular fibrous tissue has filled in a portion of the lumen present after the previous angioplasty. It appears that the initial angioplasty opened the artery considerably and probably ruptured it into the pultaceous debris shown at approximately 9:00. The fact that coronary plaques consist mainly of fibrous tissue may explain in part why angioplasty is generally successful (Figure 24).

What observations suggest that atherosclerotic plaques are the result at least in part of organization of thrombi?

There are 4 observations that suggest that atherosclerotic plaques are the result, at least in part, of organization of thrombi (47): 1) The dominant component of coronary plaques is fibrous tissue, commonly the result of organization of thrombus; 2) The presence of known components of thrombi ―namely fibrin and platelets ―within atherosclerotic plaques; 3) The occurrence of known components of atherosclerotic plaques – namely fibrous tissue, foam cells, cholesterol clefts, pultaceous debris, calcium – in organized hematomas or known thrombi wherever they might occur in the body (for example, in left atrial thrombi in mitral stenosis), and 4) The presence of multiple channels in lumens, a recognized consequence of organization of pulmonary arterial emboli.

Figures 25 shows a coronary artery stained for fibrin and bands of fibrin deposits are located more or less parallel to the margins of the lumen. A close-up of the fibrin deposits is shown in the same figure. Figure 26 is a photomicrograph of a coronary artery showing lines of demarcation (arrows) between what might be considered plaques formed at different times from organization of thrombi. The demarcation lines consist of elastic tissue which makes the separation relatively easy. Figure 27 shows a coronary artery with at least 5 revascularization channels. If one injects thrombi into a systemic vein, for example the femoral vein, these clots go into the lungs and organize and they often organize into multiluminal channels, a finding extremely common in coronary arteries, suggesting that thrombi do play a role in their organization. Figure 28 is a picture of the interior lining of the left atrium in a patient who died after mitral valve replacement (48). This patient underwent planned mitral commissurotomy without cardiopulmonary bypass about 20 years earlier but the body of the left atrium as well as its appendage was filled with thrombus and therefore the commissurotomy was not performed.

At mitral valve replacement 20 years later, the thrombus in left atrial body was absent and now the lining of the free wall consisted of typical atherosclerotic plaque containing cholesterol clefts, pultaceous debris, and dense fibrous tissue, suggesting that these "atherosclerotic plaques" resulted entirely from organization of thrombi.

Another study supporting the view that atherosclerotic plaques are formed at least in part by organization of thrombi was provided by Virmani and Roberts (48) who examined 1,290 histologic sections (1 per 5-mm segment) from 224 major epicardial coronary arteries in 57 patients with fatal CAD and compared findings with those in 27 controls: *intraplaque fibrin deposits* were present in 2% of the segments (controls <1%), in 17% of the arteries (c=3%), and in 63% of the patients (c=7%); *intraluminal thrombus*, present only in the patients with AMI and in none of the controls, occurred in 3% of the segments, in 8% of the arteries and in 26% of the patients (in 42 of the 57 patients [74%] with AMI); *intraplaque extravasated erythrocytes* were present in 10% of the segments (c=1%), in 35% of the arteries (c=4%), and in 84% of the patients (c=19%); *iron* was present in 4% of the segments (c=<1%), in 14% of the arteries (c=4%), and in 57% of the patients (c=22%).

Is atherosclerosis a multifactoral or a unifactoral disease?

Figure 29 shows 10 "atherosclerotic risk factors" and asks the question of each factor: Is this factor required to form atherosclerotic plaques? And the answer to the first 9 is "No" (49). One does not have to have the atherosclerotic gene to have atherosclerotic plaques. According to Brown and Goldstein (50), the atherosclerotic gene is present in only 1 of 500 persons. Recent studies suggest that the frequency may be half that (50). When I was in medical school I was taught that atherosclerosis was a degenerative disease, the consequence of living on planet Earth. I have had the opportunity to examine 6 hearts in patients who died when ≥100 years of age and

3 had wide open lumens and only minimal plaques. Russell Ross (51) in an article in 1986 declared that atherosclerosis was an inflammatory disease and much study has been done, particularly by the Harvard group, subsequently examining that thesis (52). If one asks, however, if an elevated C-reactive protein or another cytokine is necessary to have atherosclerosis, the answer is "No". Certainly, cigarette smoking is not healthy but cigarette smoking in and of itself does not cause atherosclerotic plaques. Although systemic hypertension and diabetes mellitus may worsen the burden, neither by itself causes plaques. One does not have to be overweight to have atherosclerotic disease. There is no evidence that exercise prevents plaques, particularly if one stops at a McDonald's on the way home from the run. What is stressful to one person is not necessarily stressful to another; it is very difficult to put a number on stress. In my view, atherosclerosis is a consequence of abnormal cholesterol levels (53-66).

What is the evidence that atherosclerosis is a cholesterol problem? There are 4 factors: 1) *Experimental evidence*. Atherosclerosis is one of the easiest diseases to produce experimentally. If one gives herbivores (rabbits, monkeys) a diet high in cholesterol and/or saturated fat, atherosclerotic plaques are produced and they are similar to those occurring in human beings. 2) *Morphologic evidence*. There is cholesterol in the plaques. 3) *Epidemiologic evidence*. The best study in my view is the Seven Countries Study headed by Ancel Keys and colleagues (67). They studied portions of populations in 7 countries and found that those populations with high levels of total cholesterol (Finland, for example) had a very high frequency of atherosclerotic events whereas those with much lower total cholesterol levels (for example, Japan) had far fewer atherosclerotic events. 4) *Therapeutic evidence*. Numerous statin trials have shown that when cholesterol levels are lowered atherosclerotic events decrease considerably (Table 5), and the lower the better (64, 68).

Although some investigators have considered cholesterol the cause of atherosclerosis for several decades, 26 authors mainly from Europe, in April 2017, published an article titled *"Low-density lipoproteins cause atherosclerotic cardiovascular disease..."* a consensus statement from the European Atherosclerosis Society Consensus Panel (66). I was glad to see the article that soundly supports the view that cholesterol is the cause of atherosclerosis. These drugs are safer than almost any drug one can put in this/her mouth.

Another very important article also appeared in March 2017, namely "*Long-term safety and efficacy in achieving very low levels of low-density lipoprotein cholesterol..."* in *JAMA Cardiology* authored by 11 prominent authors who studied 15,281 patients to determine whether achieving an LDL-cholesterol level <30 mg/dL was safe (68). The study was carried out over a 6-year period. The patients with these low levels were compared to those with higher levels. The data provides reassurance regarding the longer-term safety in patients achieving LDL-cholesterol levels <30 mg/dl. I have been on a statin (plus ezetimibe most years) for nearly 3 decades and my most recent lipid values in mg/dL were as follows: total cholesterol 102; LDL cholesterol 27; high-density lipoprotein cholesterol 68, and triglycerides 34. Some physicians worry that these very low levers are dangerous but this recent study is indeed reassuring that they are not dangerous. It appears that LDL-cholesterol levels have to be <50 mg/dL to prevent the formation of atherosclerotic plaques.

These two studies are very important in heart disease and provide clear evidence that cholesterol is the villain.

What characteristics distinguish carnivores and herbivores?

Carnivores and herbivores have different characteristics (Table 4) (69). Humans of course fit far better into the herbivore category than the carnivore category. Atherosclerosis does

not occur in carnivores and cannot be produced experimentally in carnivores unless they are previously made hypothyroid.

What are reasonable guidelines for whom to treat with lipid-altering agents?

The National Cholesterol Education Program in 1988, 1993, 2001, with revisions in 2004, and now the American Heart Association/American College of Cardiology 2013 guidelines have provided advice as to who to treat with cholesterol-lowering agents (Table 6). These treatment guidelines focus exclusively on decreasing the risk of having atherosclerotic events. They are not designed to prevent the formation of atherosclerosis plaques or to shrink those already present. My guideline is to prevent the formation of atherosclerotic plaques and to do so the LDL cholesterol needs to be <50 mg/dl, and the other risk factors must be worked on: an elevated blood pressure must be lowered, body weight must be reduced if elevated, exercise must be increased if presently avoided, and all cigarettes must be eliminated. The goal is not to decrease risk but to prevent atherosclerotic plaques! If atherosclerotic plaques are prevented, atherosclerotic consequences do not occur.

What is the Rule of 5 and the Rule of 7 in statin therapy?

The statin drugs, in my view, are the finest cardiovascular drugs ever created. The statin drugs are to atherosclerosis what penicillin was to infectious disease (57). Table 5 shows a list of 6 statin drugs and what their milligram equivalent doses are and what average reductions in total cholesterol and LDL cholesterol can be expected from those doses (58). Each time the statin dose is doubled an average of 5% additional reduction in total cholesterol occurs and an average of 7% additional reduction of LDL cholesterol occurs. The initial dose of the statin drug provides the greatest reduction in total and LDL cholesterol. With the lowest Federal Drug Administration's approved dose of any of the statin drugs there is a 22% average reduction in total cholesterol and a 27% average reduction in LDL cholesterol. Thus, the maximal dose of the

most powerful statin (rosuvastatin; 40mg) provides a 45% average total cholesterol reduction and an average 62% LDL-cholesterol reduction. That dose, however, is equivalent to 160 mg of atorvastatin and 320 mg of simvastatin. The addition of ezetimibe 10mg to the lower levels of statin doses lower LDL cholesterol an additional 18 to 25% so that the combination of ezetimibe with the lowest doses of the statin drugs leads to a 45% average LDL-cholesterol reduction. With the first doubling of the statin dose the combination leads to a 52% LDL reduction. To get that degree of LDL reduction by statin monotherapy alone it would be necessary to triple the statin dose. It is for that reason that I like the combination, statin + ezetimibe. It is well recognized that one drug rarely does the job in treating patients with systemic hypertension. That same principle, in my view, needs to be more frequently applied to lipid-lowering therapy.

What is the effect of lipid lowering drug therapy on coronary luminal narrowing?

It is never too late to begin lipid-lowering therapy. Several angiographic studies and several intracoronary ultrasound studies have shown that lumens of coronary and carotid arteries can become wider after periods of lipid-lowering therapy (64). Assuming that an individual has to have >75% cross-sectional narrowing in one or more major epicardial coronary arteries to have a coronary event, if the lumen can be widened such that it becomes <75% narrowed in cross-sectional area theoretically the flow through that widened artery is normal. There is good evidence that the lipid portion of atherosclerotic plaques can be shrunk and diminishing the quantity of lipid results in widening of the lumens. Figure 30 attempts to display that thesis graphically.

What are some requisites for a healthy life?

An LDL cholesterol <50 mg/dL; a blood pressure <115/75 mm/Hg; a body mass index <25 kg/m^2; an empty colon (orlistat 120 mg/day is useful) or better (vegetarian-fruit diet); a non-

smoking and limited alcohol lifestyle, and a bit of luck.

Conclusion

In patients with symptomatic or fatal CAD, the atherosclerotic process involves every 5-mm segment of all major (right, left main, left anterior descending, and left circumflex) epicardial coronary arteries. Likewise, when involving symptomatic or fatal aortic or peripheral arterial atherosclerosis, the process is also diffuse in those regions. Fibrous tissue is the dominant component of coronary plaques. Angioplasty works by cracking plaques. Atherosclerosis is caused by cholesterol. Four factors support the cholesterol cause of atherosclerosis. Humans fundamentally are herbivores, not carnivores. The rule of 5 and 7 is useful in statin therapy. There are at least 6 requisites for a long healthy life: an LDL cholesterol <50 mg/dl; a blood pressure <115/75 mm Hg; a body mass index <25 kg/m^2; a rapid colonic transit time (vegetarian and fruit diet and/or orlistat); no smoking or excessive alcohol, and a bit of luck.

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69. Roberts WC. We think we are one, we act as if we are one, but we are not one. *Am J Cardiol* 1990; 66:896.Figure 1. This diagram shows each of the 4 major epicardial coronary arteries and shows how each 5-mm segment is graded in cross-sectional area.

Figure 2. This diagram shows the quantity of cross-sectional area narrowing in each 5-mm segment in 27 patients with acute myocardial infarction studied at autopsy. As shown in the bottom right, 34% of the 5-mm segments were narrowed 76-100% in cross-sectional area and only 5% 25% or less, and not a single 5-mm segment was devoid of plaque.

Figure 3. This diagram shows the mean percent of 5-mm segments of each of the 4 major epicardial coronary arteries narrowed to various degrees in acute myocardial infarction: 27 patients and 1,403 5-mm segments were studied. The horizontal axis shows the 4 categories of cross-sectional area narrowing and the vertical axis shows the mean percent of 5-mm segments of coronary artery examined in the 4 coronary arteries: left main (LM); left anterior descending (LAD); left circumflex (LC), and right (R). This diagram shows that the LAD, R, and LC coronary arteries have similar degrees of narrowing at each of the 4 categories of narrowing; the LM in contrast had only 10% of the 5-mm segments narrowed >75% in cross-sectional

area. *Reproduced with permission from* Roberts WC, Jones AA. Quantification of coronary arterial narrowing at necropsy in acute transmural myocardial infarction. Analysis and comparison of findings in 27 patients and 22 controls. *Circulation* 1980; 61:786-790.

Figure 4. This diagram contrasts the quantity of coronary narrowing in a group of patients who had healed myocardial infarcts. The diagram on the left represents patients who had very large myocardial infarcts which healed and the left ventricular cavity was quite dilated. This feature is typical of course of ischemic cardiomyopathy. The diagram on the right represents a group of patients who had a myocardial infarct which healed but thereafter there was never clinical evidence of myocardial ischemia and these patients died from a non-coronary events. As shown on the bottom right the quantity of atherosclerotic plaque was similar in each of these 2 groups of patients showing that the size of a healed infarct is not helpful in determining the quantity of atherosclerotic burden.

Figure 5. This diagram shows the quantity of narrowing in each 5-mm segment in a group of patients with unstable angina pectoris who underwent coronary bypass grafting and died shortly thereafter. Although the cardiac output in these patients was entirely normal and the left ventricular cavity was of normal size and there were no myocardial scars the quantity of coronary narrowing was greater than any of the other subsets, namely 48% of the 5-mm segments were narrowed 76-100% and 29% were narrowed 51-75% in cross-sectional area.

Figure 6. This montage of Movat stained sections in each 5-mm segment of the coronary tree in a single patient with unstable angina shows severe narrowing most of the 5-mm

segments including considerable narrowing of the left main (LM) coronary artery. LAD=left anterior descending; LC= left circumflex, and RT=right. Reproduced with permission from Roberts WC, Virmani R. Quantification of coronary arterial narrowing in clinically-isolated unstable angina pectoris. An analysis of 22 necropsy patients. *Am J Med* 1979; 67:792-799.

Figure 7. Shown here are endarterectomies of the superficial femoral artery in 4 patients with severe peripheral vascular disease. Each of these endarterectomy specimens about 25 cm in length. What is shown is the atherosclerotic plaque within the lumen. There are no areas where plaque is not present. These are examples of the diffuse nature of atherosclerosis in any region in patients with either symptomatic or fatal atherosclerotic events. These 4 endarterectomy specimens were excised by Dr. Gregory Pearl of Baylor University Medical Center. The lower panel contains photomicrographs in 18 of the 28 five-mm sections prepared from the superficial femoral artery shown at the bottom of the 4 upper specimens. The cross-sections proximally are represented by the earlier alphabetic letter and those more distally by the later letters. Thrombus with ruptured plaque is seen in *a* through *d*. Additional thrombus without underlying plaque rupture is seen in *e*. In *j* and *k*, the lumen is totally occluded mainly by fibrous plaque. Media is present circumferentially on all sections, indicating that the operative dissection plaque was in the media. All sections contain plaque. Movat stains, X 100. The patient was a 60-year-old man who had debilitating claudication. At age 44 he had had percutaneous coronary intervention because of angina pectoris and at age 58 he had coronary bypass because of recurrence of angina. The bottom endarterectomy specimen and the

photomicrographs are reproduced with permission from Roberts WC, Ko MK, and Pearl GP. *Am J Geriatric Cardiol* 2008; 17:50-52.

Figure 8. Shown here is an endarterectomy specimen of the entire right coronary artery in a patient who had severe narrowing not only of the right but also of the left anterior descending and left circumflex coronary artery. The ostium of the right coronary artery is shown at the bottom and at the top is a little posterior descending branch. This endarterectomy specimen shows that the atherosclerotic process is continuous and there are not areas where plaque is not present. Reproduced with permission from Roberts WC, Turnage TA II, Whiddon LL. Quantitative comparison of amounts of cross-sectional area narrowing in coronary endarterectomy specimens in patients having coronary artery bypass grafting to amounts of narrowing in the same artery in patients with fatal coronary artery disease studied at necropsy. *Am J Cardiol* 2007; 99:588-592.

Figure 9. This diagram shows the differences between the units of angiography which is diameter reduction vs. the units of echocardiography or autopsy which is cross-sectional area. The angiogram compares an area of considerable narrowing to an adjacent area which is assumed to be normal. Cross-sectional area is most easily measured if the circle is divided into 4 quadrants. In general, a 50% diameter reduction is equivalent to a 75% cross-sectional area narrowing.

Figure 10. Shown at the top is a diagram showing how the units of angiography *top right* compare to the units of cross-sectional area. The top panel assumes that the area of narrowing is compared to an adjacent area which is normal. That scenario however rarely if ever exists. The more likely scenario is shown in the bottom diagram such

that an area of severe narrowing is simply compared to an adjacent area which is less narrowed but not normal. Reproduced with permission from Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: Comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979; 91:350-356.

Figure 11. Shown here is an angiogram of the right coronary artery in a patient who has severe narrowing of the LAD and LC coronary arteries. A coronary bypass operation was planned with conduits to be inserted in the LC system and in the LAD coronary artery. The right coronary artery was preoperatively judged to have some irregularity but not enough narrowing to warrant the insertion of a conduit. Unfortunately, this patient died 3 days after the bypass operation and 5-mm segments were prepared from that right coronary artery at autopsy and they are shown in Figure 12.

Figure 12. Shown here are Movat-stained cross-sectional areas of each 5-mm segment of the right coronary artery whose angiogram is shown in Figure 11. The numbers are centimeters from the ostium of the right coronary artery. Each of these 5-mm segments contains plaque but most of the lumens extend from one wall of the aorta to the opposite wall and the contrast material is in the lumen and if the diameter of the lumen is roughly normal the angiogram can appear to be free or relatively free of underlying plaque. Segment 8.5 cm from the ostium is relatively narrowed.

Figure 13. This diagram shows a heart under the surface of the water with the great arteries protruding above the surface. The point of this picture is to emphasize that most of the atherosclerotic plaque in the coronary arteries is not seen well by angiogram.

Figure 14. Shown on this bar graph showing various components of the atherosclerotic plaque in

a number of patients with fatal coronary artery disease. The horizontal axis shows the degrees of cross-sectional area narrowing and the vertical axis shows the percent of the 5-mm segments narrowed to each of these 5 categories. The combination of dense, loose, and cellular fibrous tissue is by far the dominant component of the coronary plaques irrespective of the degree of cross-sectional area narrowing. Pultaceous debris and calcified fragments were not observed unless the lumen was narrowed >50% in cross-sectional areas.

Figure 15. Shown in this bar graph are coronary arteries in 9 patients with fatal juvenile diabetes. The average age of onset in these 9 patients was 9 years and the average age of death was 29 years. The code in this diagram is different from that in Figure 14. The red represents dense fibrous tissue and the yellow represents cellular fibrous tissue and the diagram shows that irrespective of the quantity of cross-sectional area narrowing fibrous tissue is the dominant component of the atherosclerotic plaque. Pultaceous debris (extracellular lipid) was excessive only in the patients in whom the luminal narrowing was extremely severe (>75% in cross-sectional areas). Reproduced with permission from Mautner GC, Mautner SL, Lin F, Roggin GM, Roberts WC. Amounts of coronary arterial luminal narrowing and composition of the material causing the narrowing in Buerger's disease. *Am J Cardiol* 1993; 71:486-490.

Figure 16. This diagram shows the relation of plaque composition relative to the degrees of cross-sectional area of luminal narrowing. Shown on the left are bars at various degrees of cross-sectional area narrowing in saphenous venous conduits studied at autopsy compared to the cross-sectional area narrowing and composition of the plaques in the native coronary arteries. The plaques in the saphenous venous grafts

again show that fibrous tissue is the dominant component whether it is cellular or dense. It took approximately 80 months for the atherosclerotic plaques in the saphenous venous grafts to look like the plaques in the native coronary arteries. Reproduced with permission from Mautner SL, Mautner GC, Hunsberger SA, Roberts WC. Comparison of composition of atherosclerotic plaques in saphenous veins used as aortocoronary bypass conduits with plaques in native coronary arteries in the same men. *Am J Cardiol* 1992; 70:1380-1387.

Figure 17. This diagram compares the composition of the atherosclerotic plaques in women versus men in native coronary arteries and in saphenous venous grafts. It shows that the quantity of dense fibrous tissue in women in both native coronary arteries and in saphenous venous graft is less than in the men. Reproduced with permission from Mautner SL, Lin F, Mautner GC, Roberts WC. Comparison in women versus men of composition of atherosclerotic plaques in native coronary arteries and in saphenous veins used as aortocoronary conduits. *J Am Coll Cardiol* 1993; 21:1312-1318.

Figure 18. This diagram shows how the study to be described in Figure 19 was carried out. The study involved studying the native coronary arteries by the 5-mm segment approach in native arteries which were bypassed and in native arteries which were not bypassed to ask if there was differences in the degrees of cross-sectional area narrowing. Reproduced with permission from Waller BF, Roberts WC. Amount of narrowing by atherosclerotic plaque in 44 nonbypassed and 52 bypassed major epicardial coronary arteries in 32 necropsy patients who died within 1 month of aortocoronary bypass grafting. *Am J Cardiol* 1980; 46:956-962.

Figure 19. This bar graph compares the quantity of narrowing in 5-mm segments by plaque in

bypassed (B) (226 coronary arteries) and non-bypassed (NB) (80 coronary arteries) in 102 patients dying early (65 patients) or late (37 patients) after aorto-coronary bypass grafting. Whether the patients died early (≤60 days) or later the quantity of plaque in the 5-mm segments of both native bypassed and non-bypassed arteries were similar. Reproduced with permission from Waller BF, Roberts WC. Amount of narrowing by atherosclerotic plaque in 44 nonbypassed and 52 bypassed major epicardial coronary arteries in 32 necropsy patients who died within 1 month of aortocoronary bypass grafting. *Am J Cardiol* 1980; 46:956-962.

Figure 20. This is a photograph of a coronary artery which had undergone coronary angioplasty at this site. The plaque is cracked and a small dissection is apparent.

Figure 21. Shown here is a photomicrograph of a coronary artery at the site of coronary angioplasty. The atherosclerotic plaque is cracked and a dissection is created between the internal elastic membrane and overlying intimal plaque. Movat stain, X 40.

Figure 22. Shown here are photomicrographs of cross-sectional areas at sites of previous coronary angioplasty in 6 different patients. The arrows show where cracks in plaque occurred. Movat stains, X 20 (a, b); X 27 (c, d); X14 (e, f); X22 (g, h). Reproduced with permission from Potkin BN, Roberts WC. Effects of percutaneous transluminal coronary angioplasty on atherosclerotic plaques and relation of plaque composition and arterial size to outcome. *Am J Cardiol* 1988; 62:41-50.

Figure 23. Shown is a photomicrograph of a coronary artery which had coronary angioplasty several months earlier. Surrounding the lumen is fibromuscular tissue which is quite different from the underlying dense fibrous tissue shown closer to the media. The

angioplasty procedure appeared to have ruptured the plaque to area of pultaceous debris located at approximately 11:00 and another plaque shown at approximately 6:00. The introduction of stents wouldn't prevent or lessen this neo-intimal fibromuscular proliferation.

Figure 24. Shown here is a diagram of plaque composition in patients having coronary angioplasty and the 5-mm segments at sites of angioplasty were determined for composition. The green represents fibrous tissue, the blue, extracellular lipid, and the pink, calcium. Whether there was early or late or success or early failure, fibrous tissue was the dominant component at the site of the angioplasty.

Figure 25. Shown on the *left* is a section of coronary artery showing some purple lines parallel to one another and near the lumen of the artery and a more peripheral portion of the artery consists of dense fibrous tissue. Shown on the *right* is a close up of one area marked off in the left diagram showing fibrous tissue, fibrin, fibrous tissue, fibrin, suggesting that the fibrous tissue at least in part was the result of organization of fibrin by far the dominant component of thrombus. Reproduced with permission from Roberts WC. Does thrombosis play a major role in the development of symptom-producing atherosclerotic plaques? *Circulation* 1973; 48:1161-1166.

Figure 26. Shown here is a cross-section of a coronary artery showing various lines of demarcation separating possibly one plaque from another plaque suggesting that possibly thrombus was laid down and then organized and then laid down again and then organized.

Reproduced with permission from Roberts WC. Does thrombosis play a major role in the development of symptom-producing atherosclerotic plaques? *Circulation* 1973;

48:1161-1166.

Figure 27. Shown here is a coronary artery with 4 revascularized channels, something commonly seen when thrombus organizes in various arterial systems. These multi-luminal channels are seen in about 5% of coronary trees when studied by the 5-mm segment approach.

Figure 28. Shown here is the wall of left atrium in a patient who had severe mitral stenosis and underwent planned mitral commissurotomy 20 years earlier. When the surgeon entered the pericardial space he found that the entire left atrial body and appendage was filled with thrombus and since there was no cardiopulmonary bypass available at the time, the thoracotomy was closed. Twenty years later the same patient returned for a mitral valve replacement and now there was no thrombus in the left atrial cavity but the left atrial wall contained classic heavily classified atherosclerotic plaques, a bit of evidence that one can start with a thrombus and end with a plaque. Reproduced with permission from Roberts WC. Does thrombosis play a major role in the development of symptom-producing atherosclerotic plaques? *Circulation* 1973; 48:1161-1166.

Figure 29. Shown here are various atherosclerotic risk factors and the question is asked, "Is each necessary to form plaques?" The only one where the answer is "Yes" is an elevated cholesterol level. Reproduced with permission from Roberts WC. Atherosclerotic risk factors: are there ten or is there only one? *Am J Cardiol* 1989; 64:552-554.

Figure 30. This diagram shows the theoretical situation if one lowers one's LDL cholesterol considerably. It appears that the lipid portion of plaques is reversible if the LDL cholesterol levels are severely lowered. If an atherosclerotic plaque narrows a lumen

>75% in cross-sectional area flow through that artery is limited. If the plaque can be reduced such that the lumen is <75% narrowed in cross-sectional area, flow through that lumen theoretically is relatively normal.

Table 1.

MODES OF DEATH IN FATAL CORONARY ARTERY DISEASE
(889 Necropsy Patients ≥30 Years of Age)

Modes of Death	Numbers (%)
I. Acute Myocardial Infarct (MI) (Healed MI=119 [28%])	426 (48)
II. Sudden Out-of-Hospital Death (Healed MI=118 [49%])	239 (27)
III. Chronic HF + Healed MI (LV aneurysm = 33 [19%])	170 (19)
IV. Sudden In-Hospital Death (Unstable angina = 35 [67%]) (Healed MI = 30 [55%])	55 (6)
TOTALS	**889 (100)**

HF = heart failure; LV = left ventricular

Table 2. Quantitative Studies (Five-mm Segments of all 4 Major Epicardial Coronary Arteries) on Amounts of Coronary Narrowing in Patients with Coronary Events

Subgroup (Reference)	Year Published	No. Pts	Men	Mean Age (Yrs)	No. 5-mm Segments	N 0 - 25
I. SUDDEN CORONARY DEATH						
A. All sudden coronary deaths	1984	60	60	51	2,995	546 (
B. With -vs- without coronary thrombus						
With	1984		12	43	639	173 (2
Without	1984	57	45	57	2,845	541 (1
C. Cath Lab death with angina pectoris	1981	10	7	47	354	23 (6
D. With -vs- without previous cardiac event	1984	70	63	50		
Previously symptomatic		31			1,493	223 (1
Previously asymptomatic		39			1,991	498 (2
II. ACUTE MYOCARDIAL INFARCTION (MI) - ALL	1980	27	21	50	1,403	285 (2
III. HEALED MYOCARDIAL INFARCTION	1982	56	52	62	2,424	212 (9
A. Ischemic cardiomyopathy	1986	56	53	62	2,999	804 (2
B. LV aneurysm after healed MI	1980	22	19	62	992	40 (4
C. Healed MI and non-cardiovascular death	1981	18	15	66	924	101 (1

D. Anterior -vs- Posterior MI	1985	59							
Anterior wall	1982	22	15		895	79 (9%)	173 (19%)	303 (34%)	340 (
Posterior wall	1982	37	27		1,713	134 (8%)	229 (13%)	560 (33%)	790 (
E. Clinically recognized -vs- unrecognized MI	1982	61							
Clinically recognized	1982	33			1,443	84 (6%)	230 (16%)	519 (36%)	611 (
Clinically silent	1982	28			1,262	139 (11%)	197 (16%)	374 (30%)	552 (
F. Small -vs- large healed MI	1982								
Small	1982	28	21	62	1,260	136 (11%)	195 (15%)	394 (31%)	535 (
Large	1982	28	21	62	1,229	76 (6%)	186 (15%)	443 (36%)	524 (
IV. UNSTABLE ANGINA PECTORIS WITH DEATH AFTER CORONARY BYPASS		22	13	48	1,049	119 (11%)	454 (48%)	305 (29%)	497 (
V. JUVENILE DIABETES MELLITUS	1978	9	6	29	382	116 (31%)	85 (22%)	123 (32%)	58 (1

Table 3. **Frequency of Acute Coronary Lesions and of Multiliminal Channels at *In Patients* with Unstable Angina Pectoris (UAP), Sudden Coronary Death (SCD) and Acute Myocardial Infarction (AMI)**

Coronary Subset	Number of Patients	Coronary Arteries			
		Thrombi	Plaque Rupture	Plaque Hemorrhage	Multiluminal Channels
UAP	14	4 (29%)*	5 (36%)*	3 (21%)*	14 (100%)
SCD	21	6 (29%)*	4 (19%)*	4 (19%)*	17 (81%)
AMI	32	22 (69%)**	24 (75%)**	20 (63%)**	29 (90%)
Totals	67	32 (48%)	33 (49%)	27 (40%)	60 (90%)

*-** = p<.02

Table 4. Differences in Carnivores and Herbivores.

Characteristics	Carnivores	Herbivores
Appendages	Claws	Hands or hoofs
Teeth	Sharp	Flat
Intestines	Short	Long
Body cooling	Pant	Sweat
Drinking water	Lap it	Sip it
Vitamin C	Make it themselves	Obtained solely from diet

Table 5. Statin Therapy – Rule of 5 and 7

STATIN THERAPY – RULE OF 5 AND 7

mg equivalent dose						⑤ ↓ TC	⑦ ↓ LDL	E 10 mg ↓ LDL	Total LDL ↓
R	A	S	P	L	F				
1.25	5	10	20	20	40	22%	27%	18%	45%
2.5	10	20	40	40	80	27%	34%	18%	52%
5	20	40	80	80	-	32%	41%	14%	55%
10	40	80	-	-	-	37%	48%	12%	60%
20	80	-	-	-	-	42%	55%	10%	65%
40	-	-	-	-	-	45%	62%	10%	72%

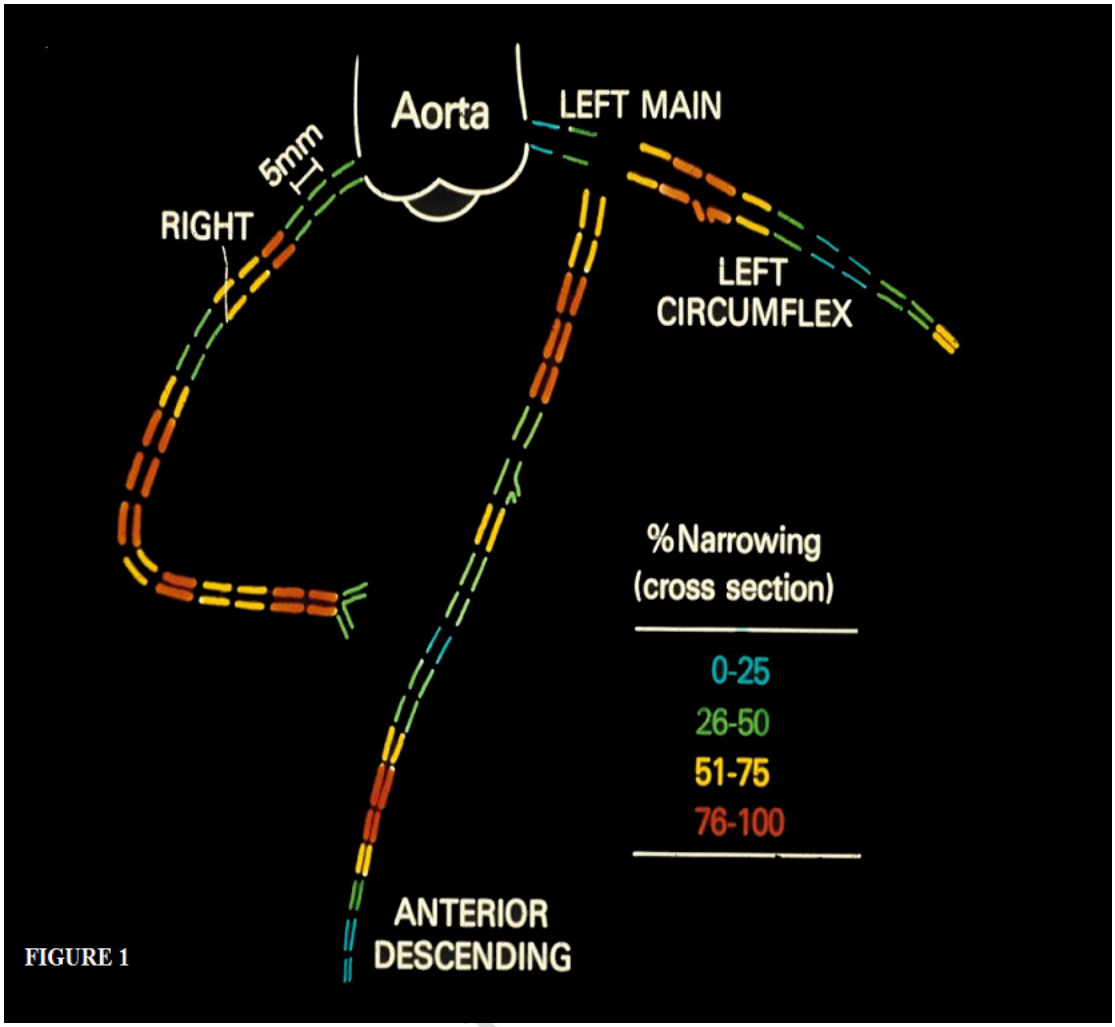
Abbreviations: A=atorvastatin; E=ezetimibe; F=fluvastatin; L=lovastatin; LDL=low-density lipoprotein cholesterol; P=pravastatin; R=rosuvastatin; S=simvastatin; TC=total cholesterol

Table 6. **Shown in this diagram are guidelines for who to treat with lipid-altering drugs at various times. These guidelines are an attempt to decrease risk of an atherosclerotic event, not to prevent atherosclerotic plaques from forming. Much lower levels of low-density lipoproteins (LDL) will be necessary to prevent plaques.**

Drug Guidelines (To decrease risk)

LDL (mg/dL)	Other RF	Goal
>190	≤1	<160
>160	>1	<130
>130	HA	<100 (<70)

HA=heart attack; RF=risk factor



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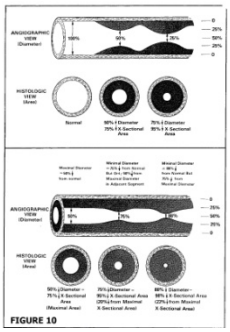

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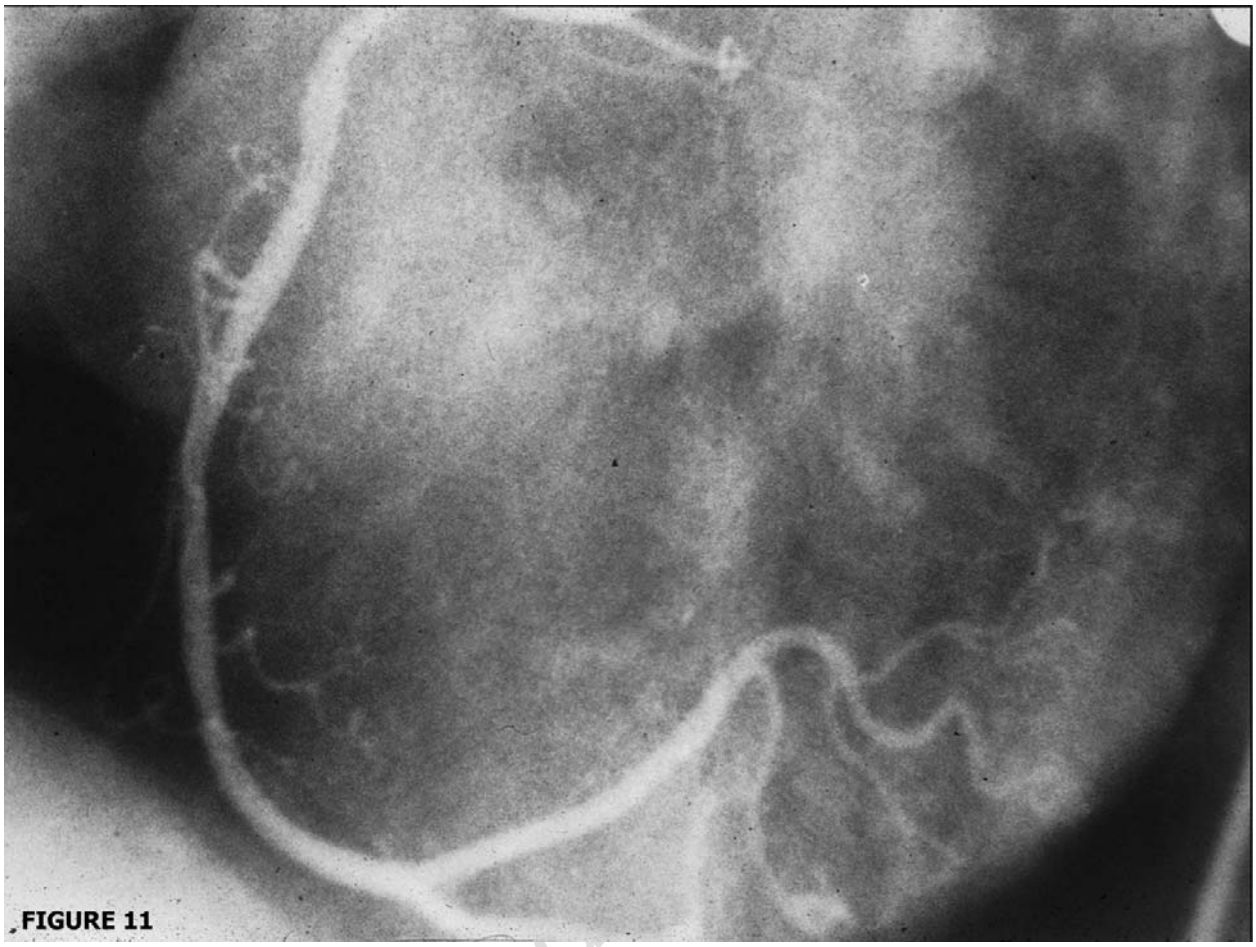

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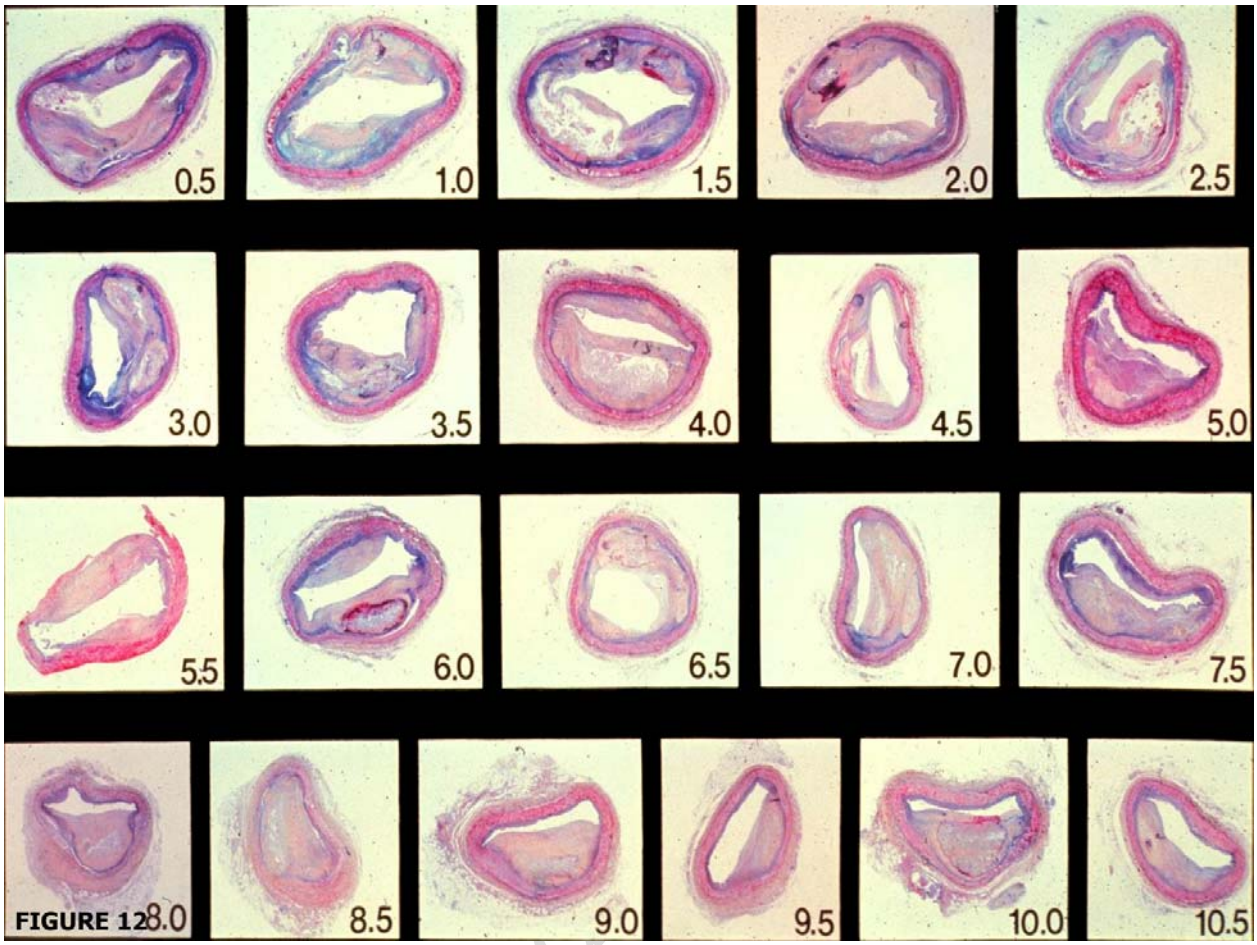

FIGURE 12

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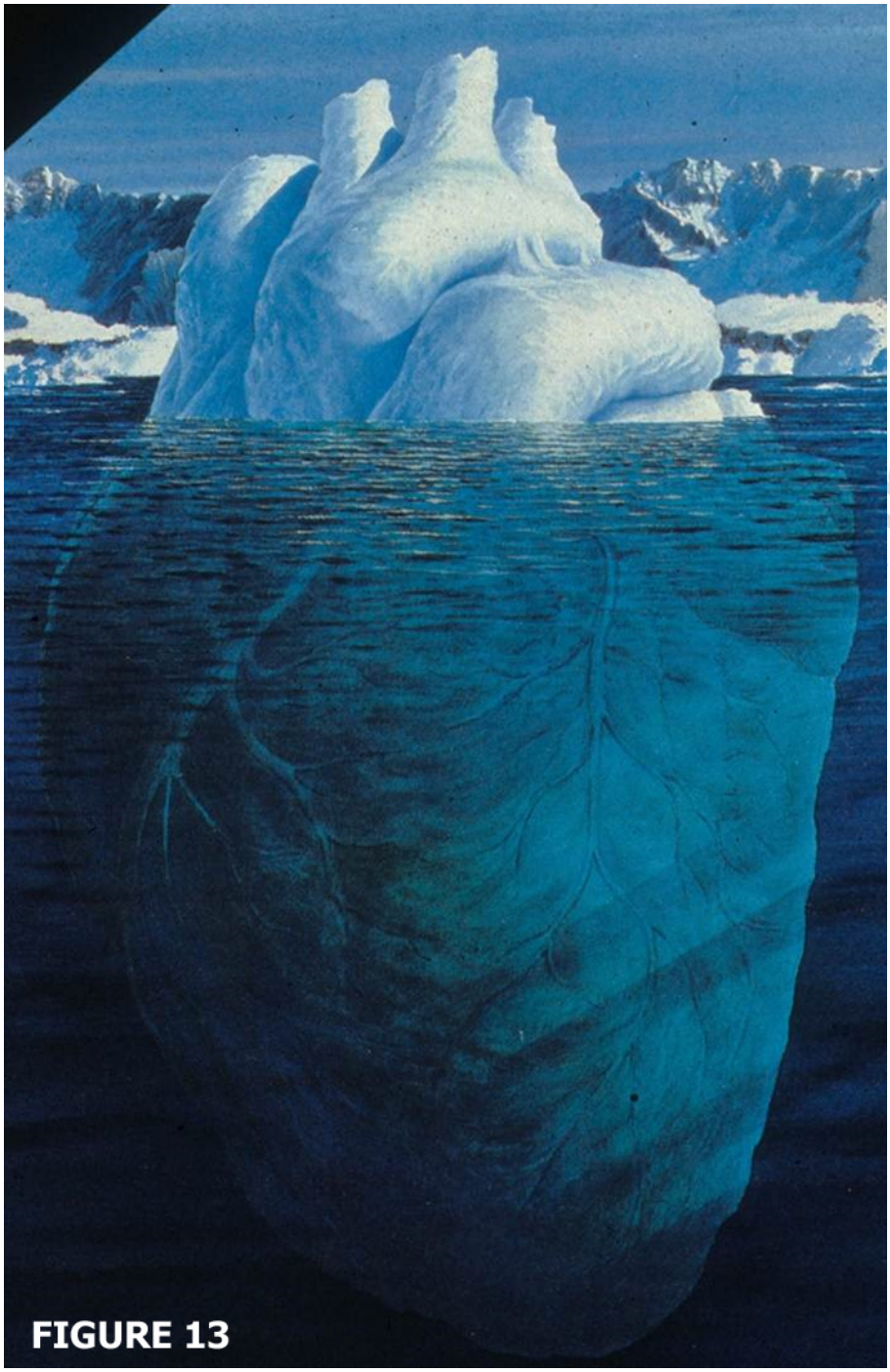

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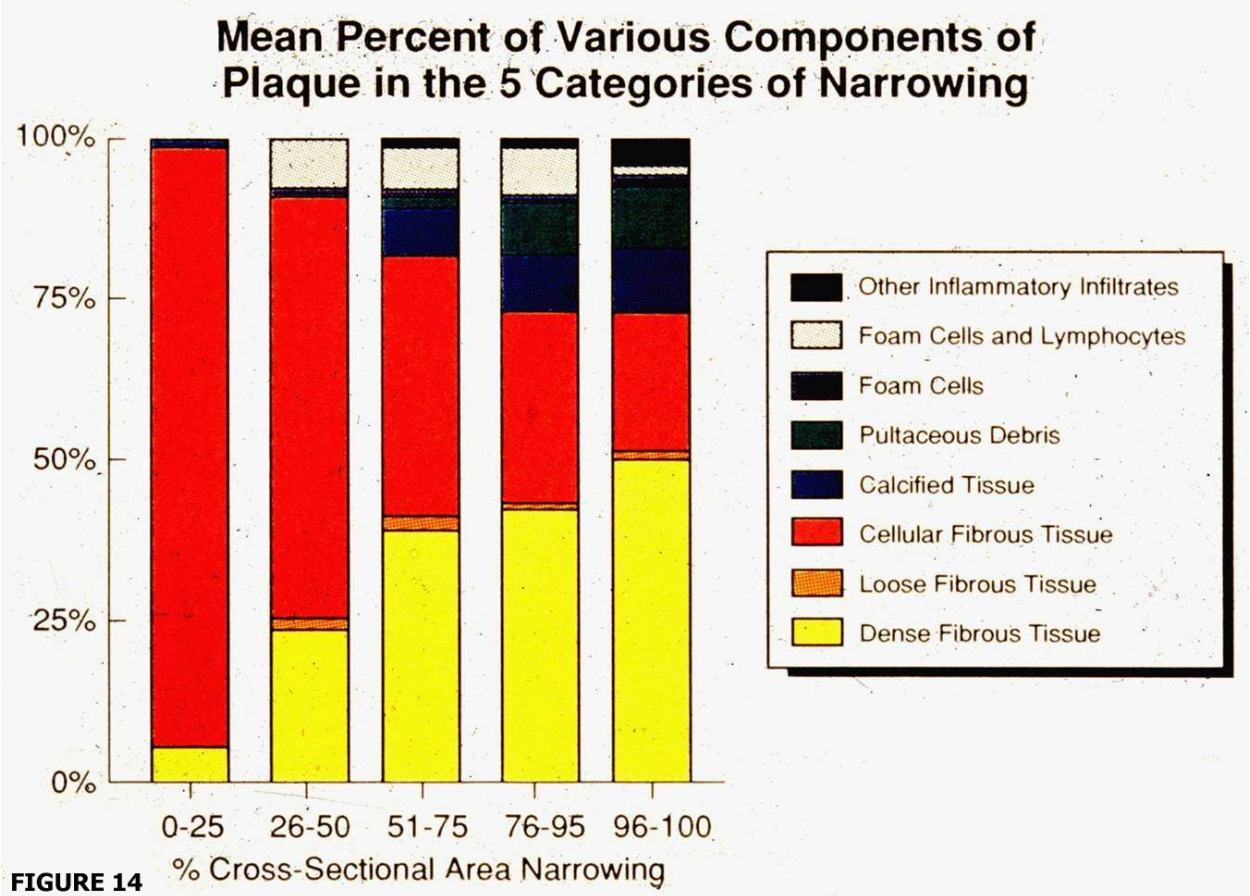

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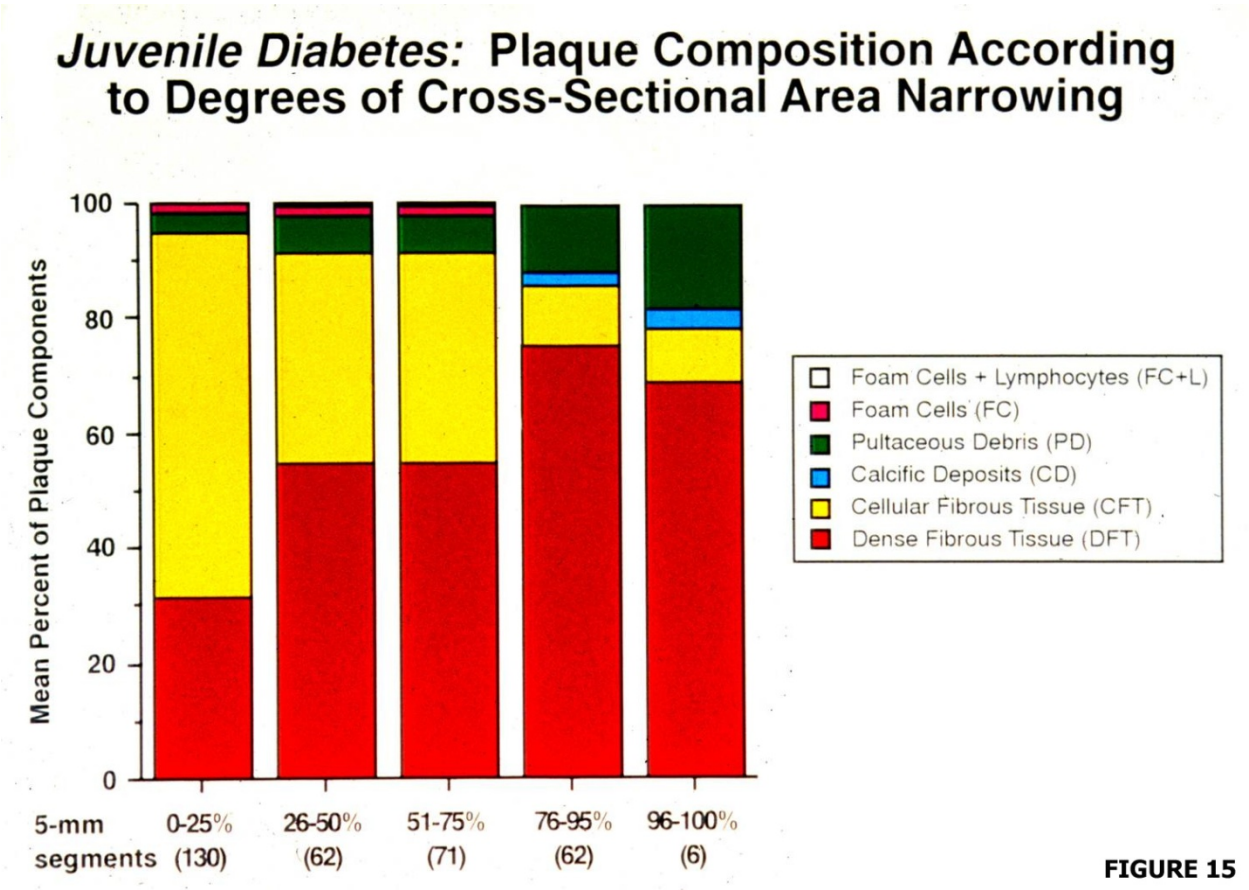

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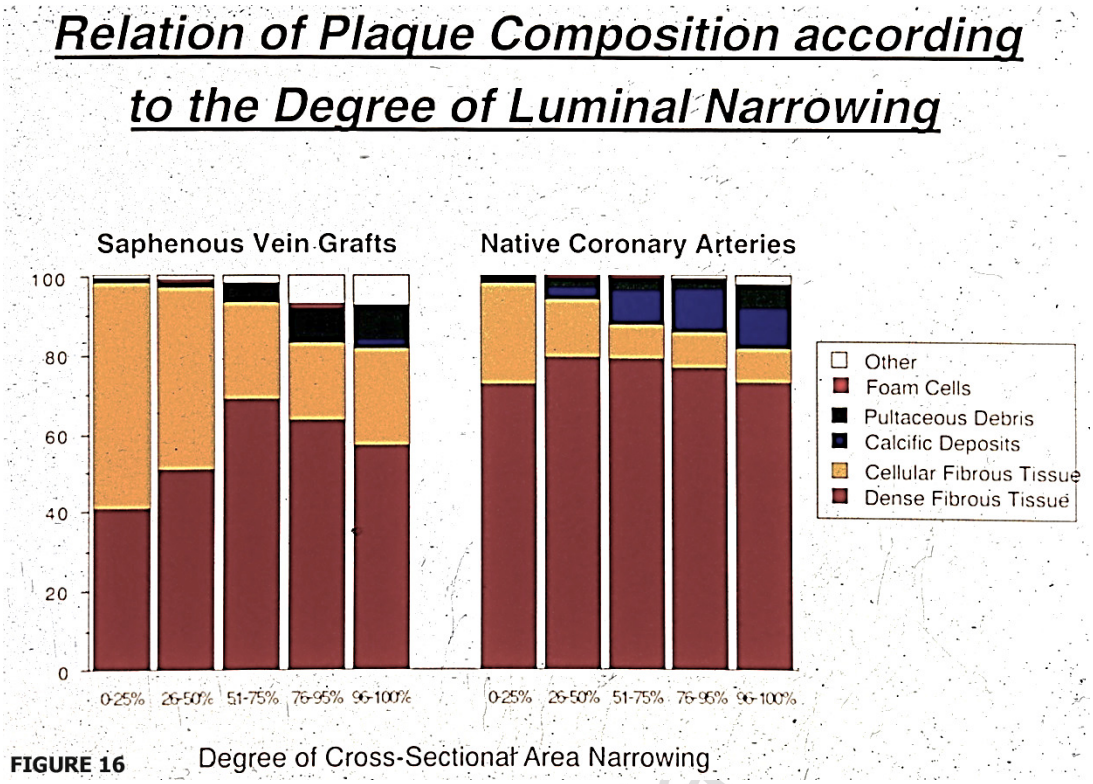

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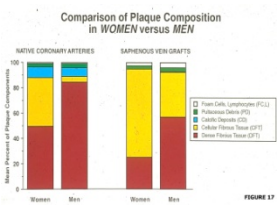

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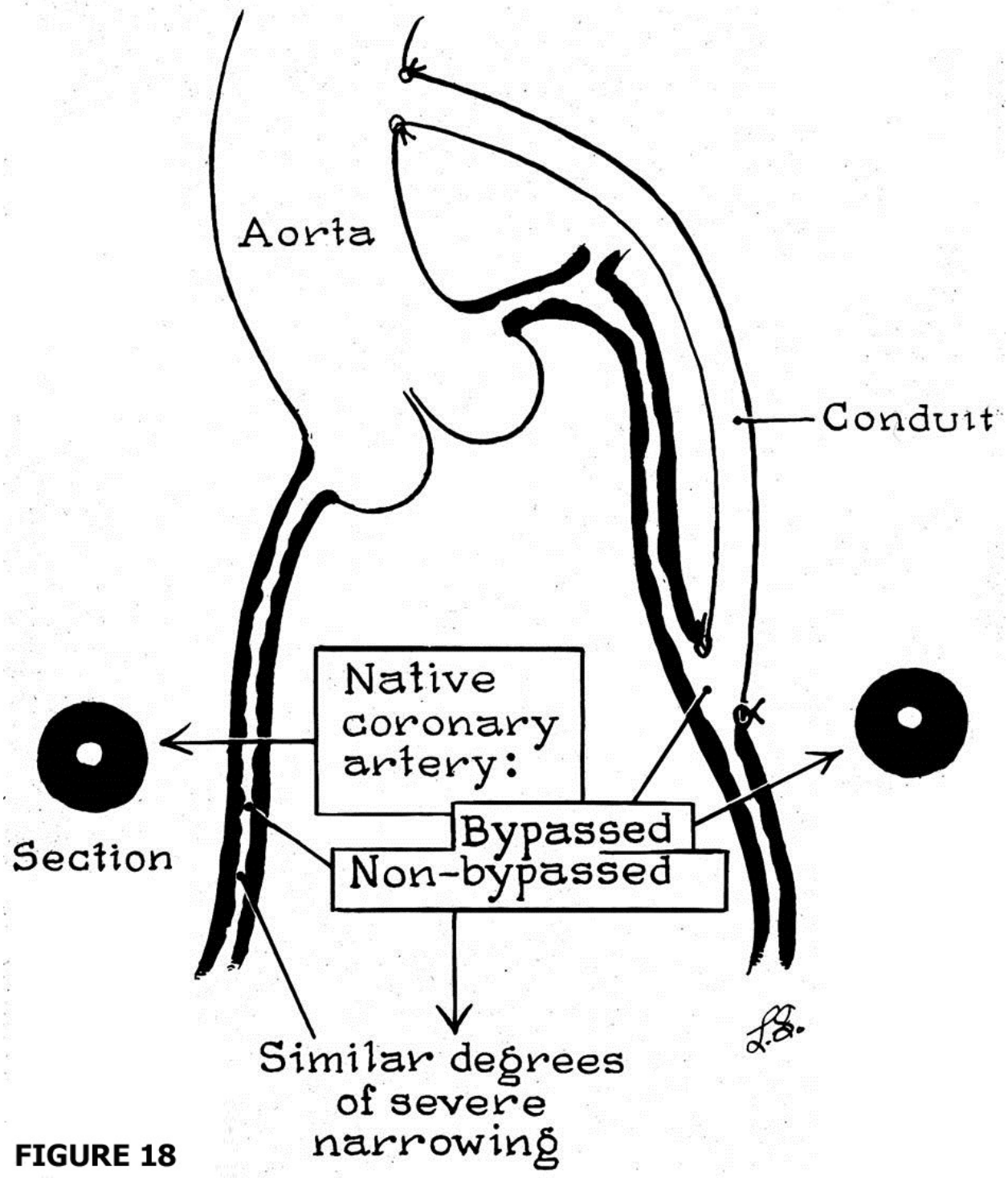

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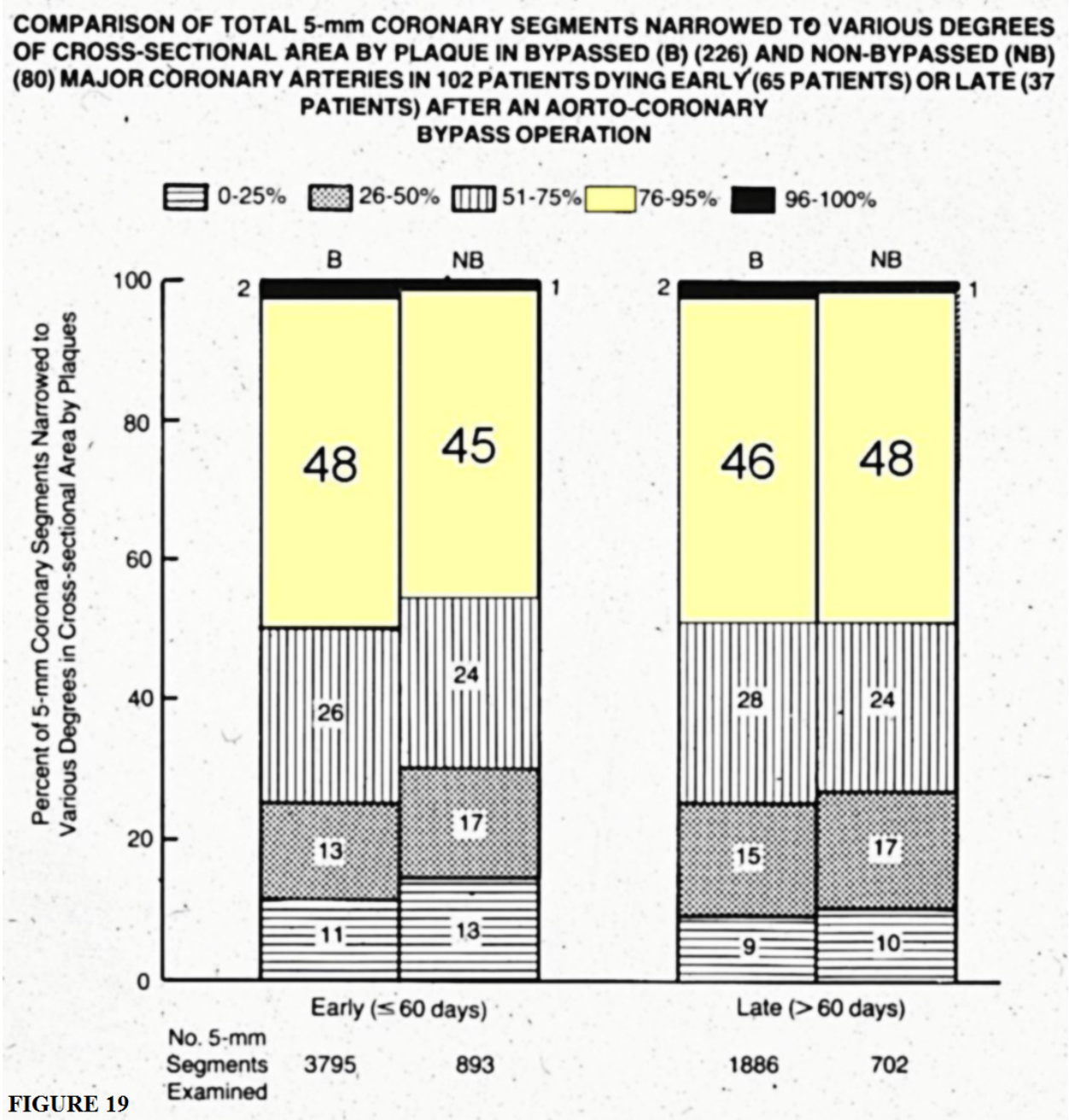

FIGURE 19

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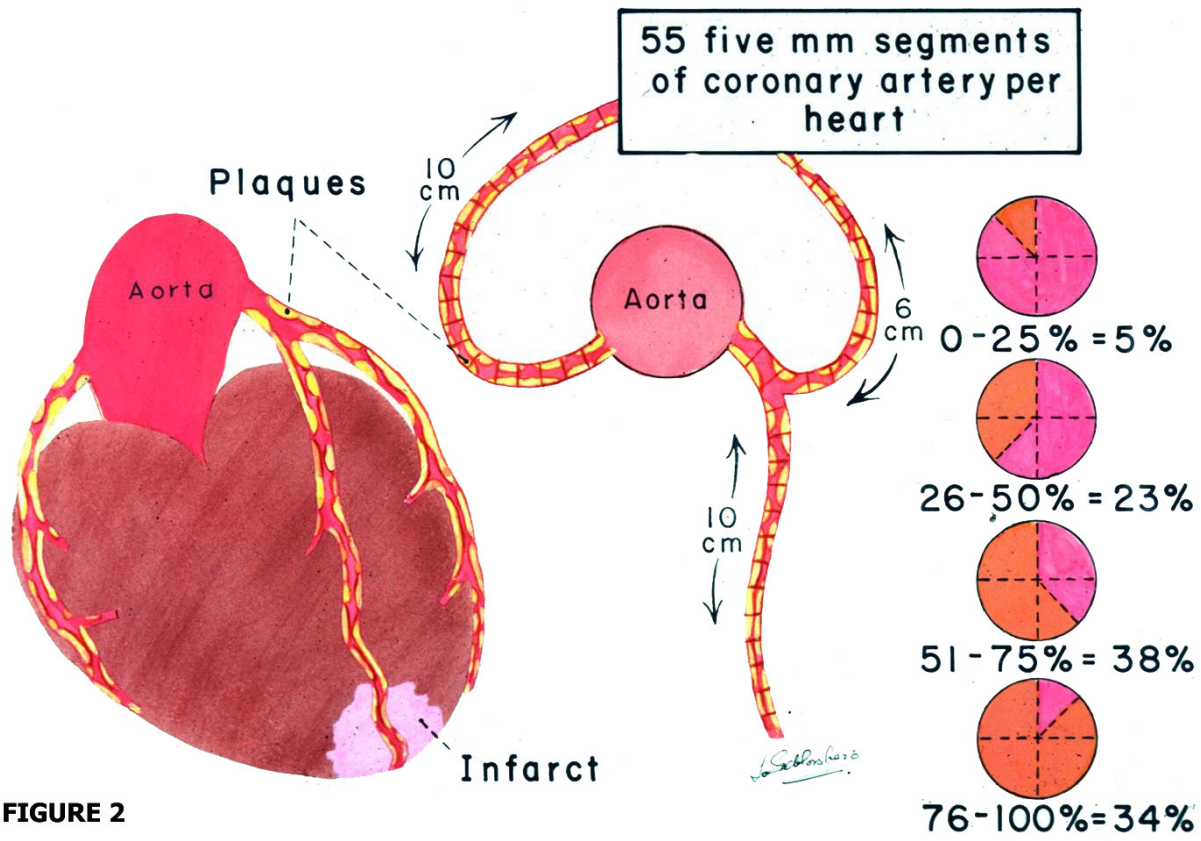

FIGURE 2

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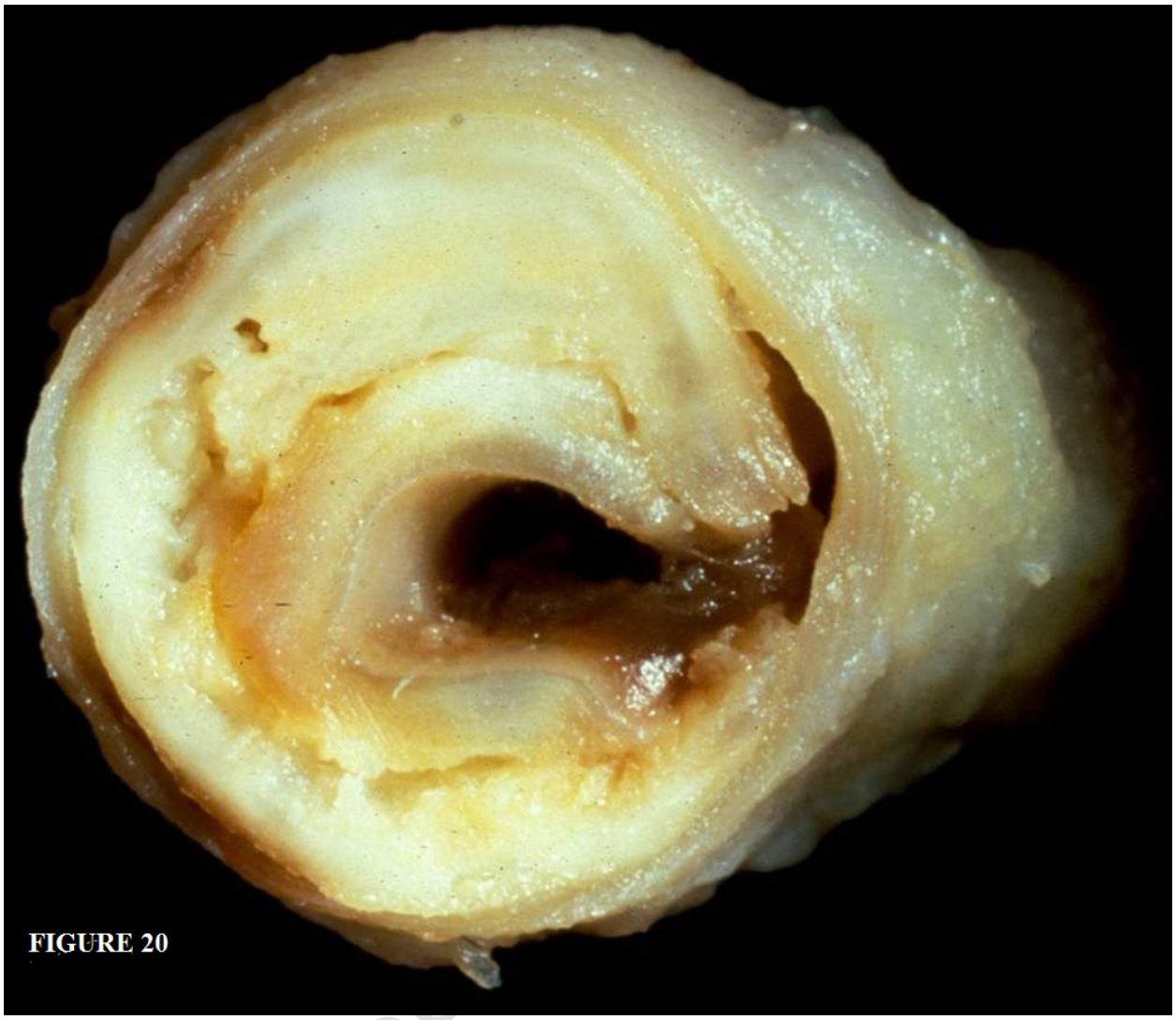

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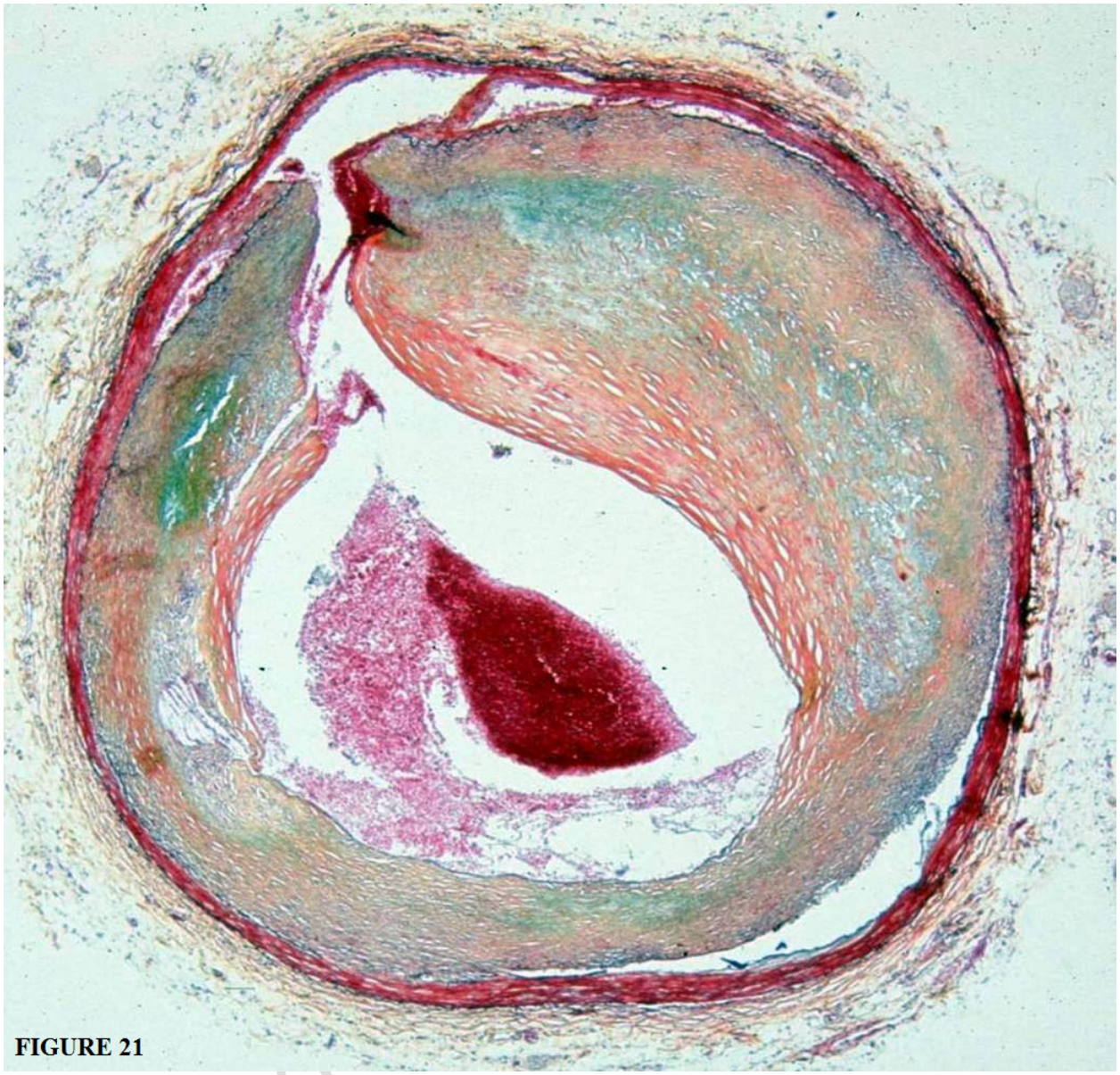

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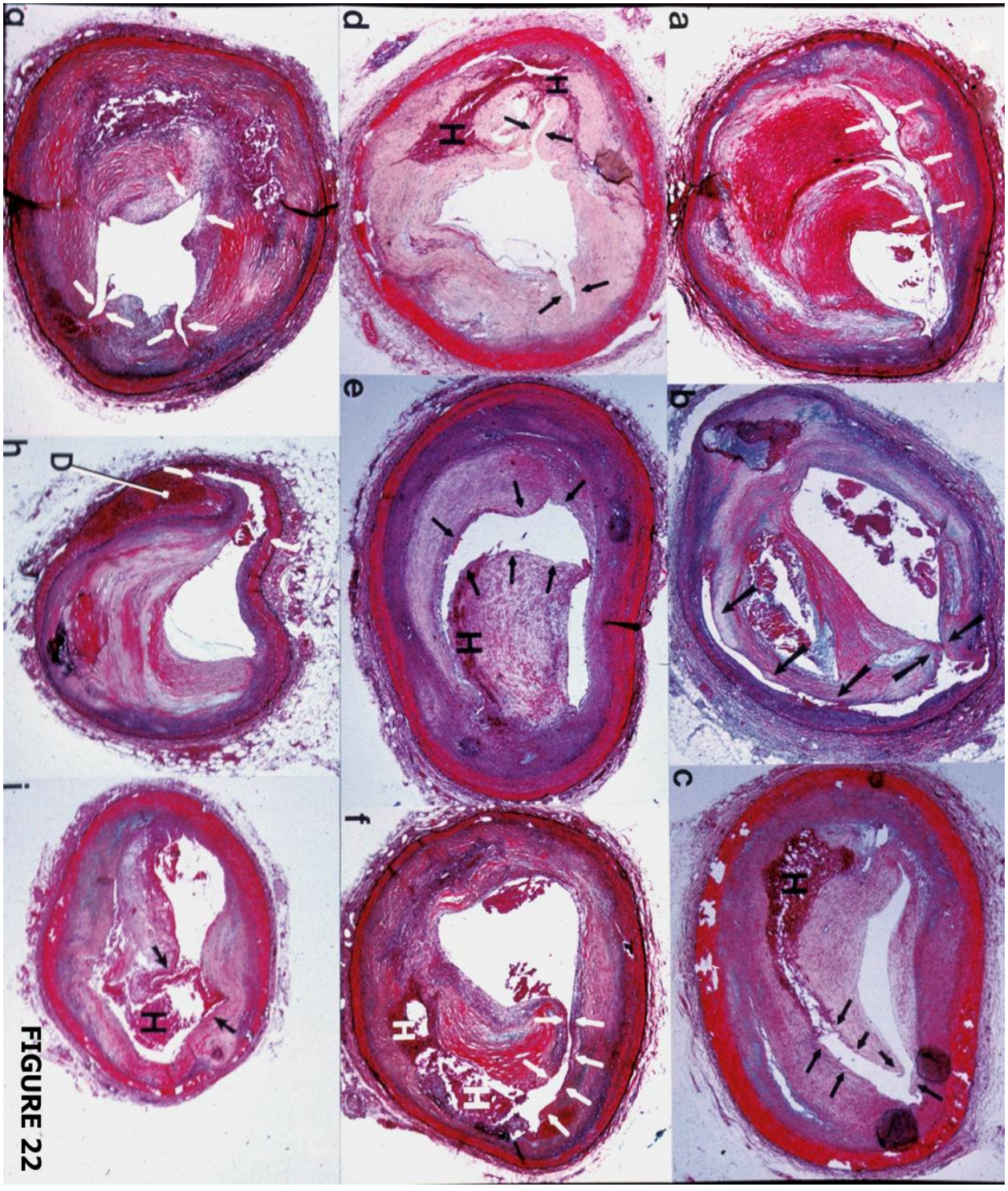

FIGURE 22

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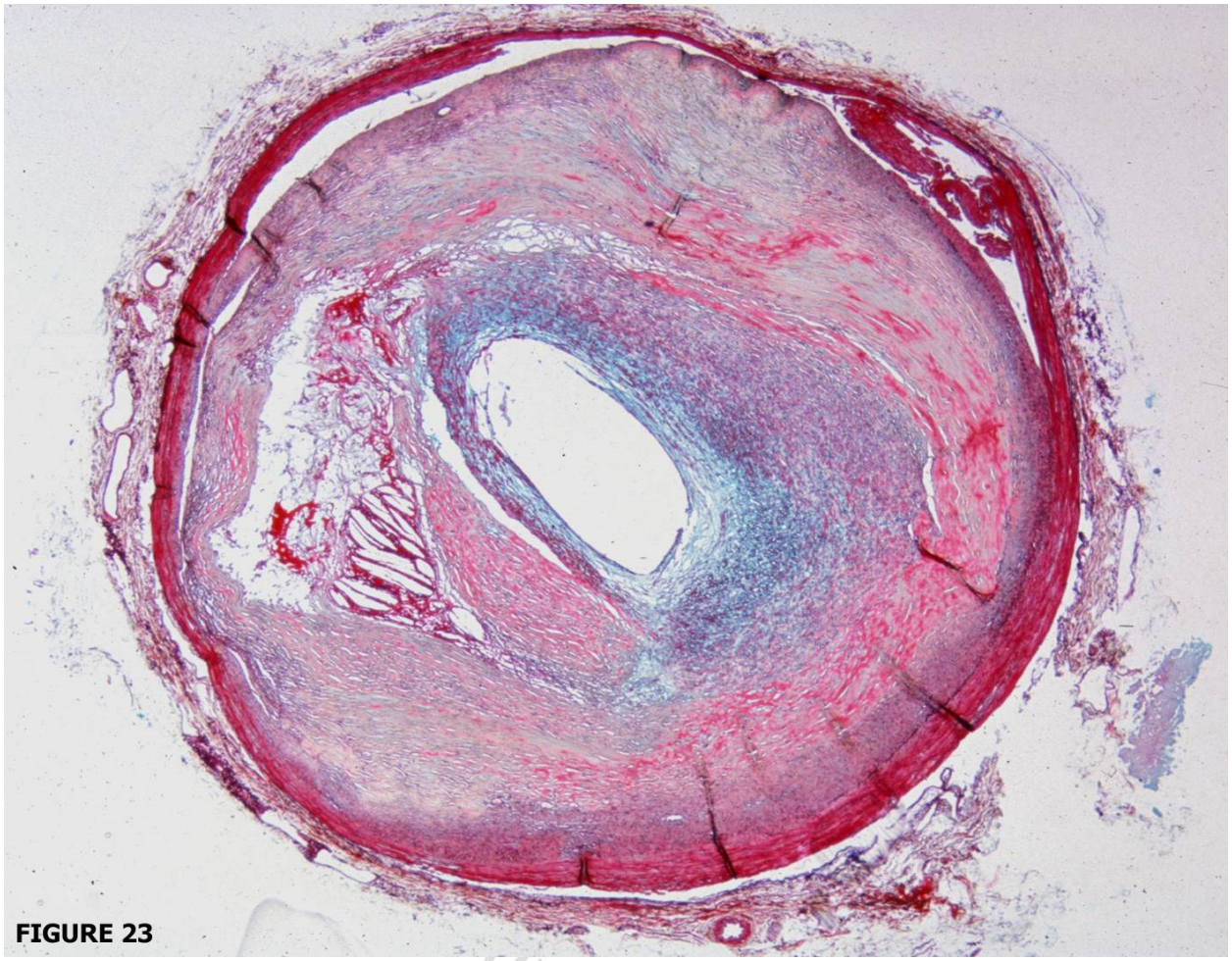

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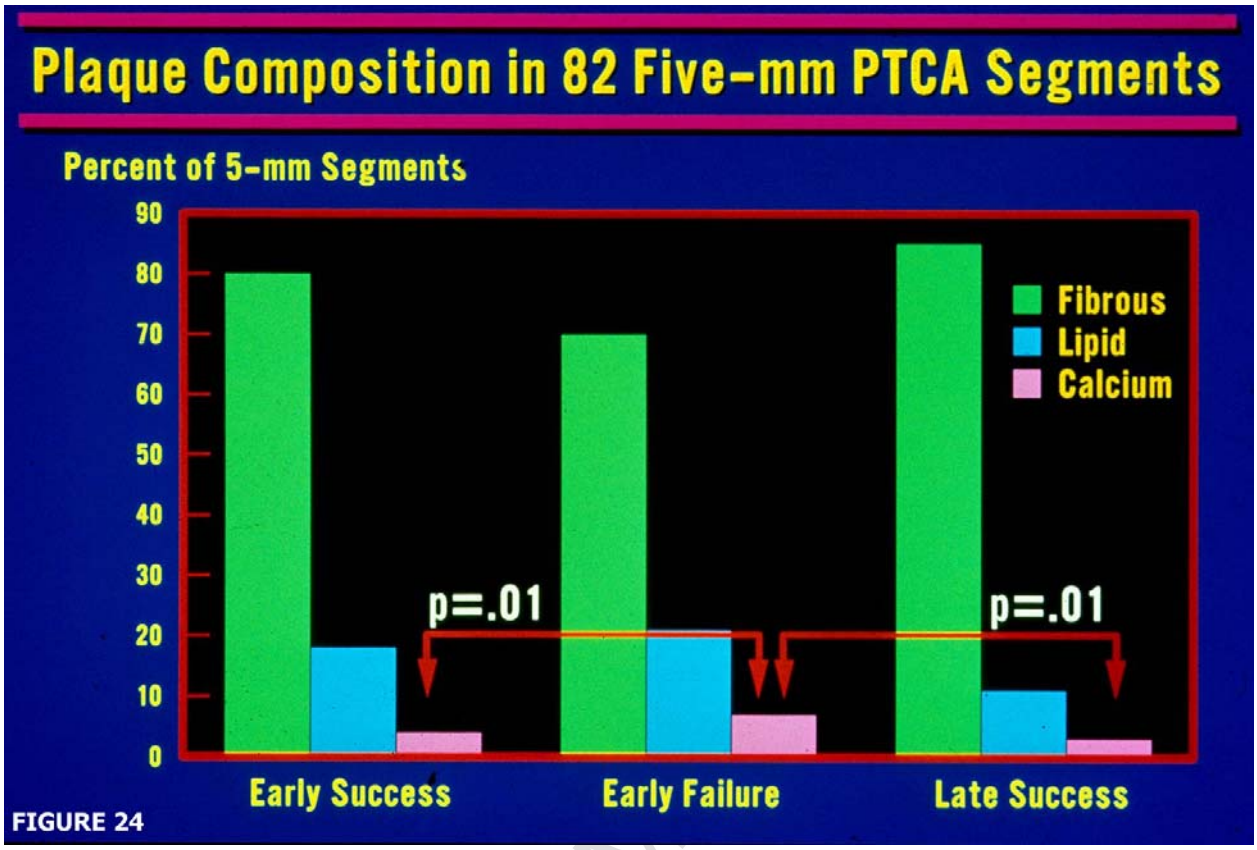

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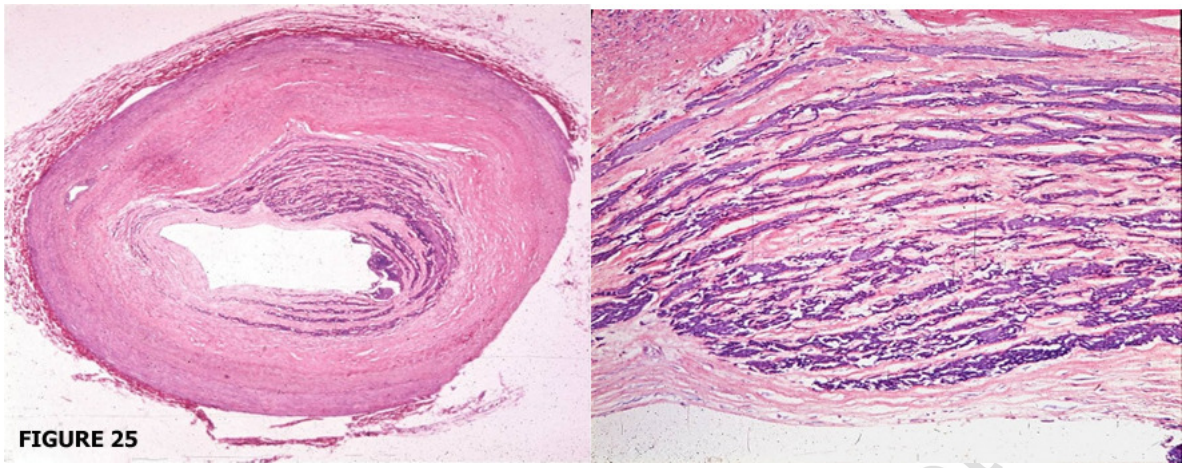

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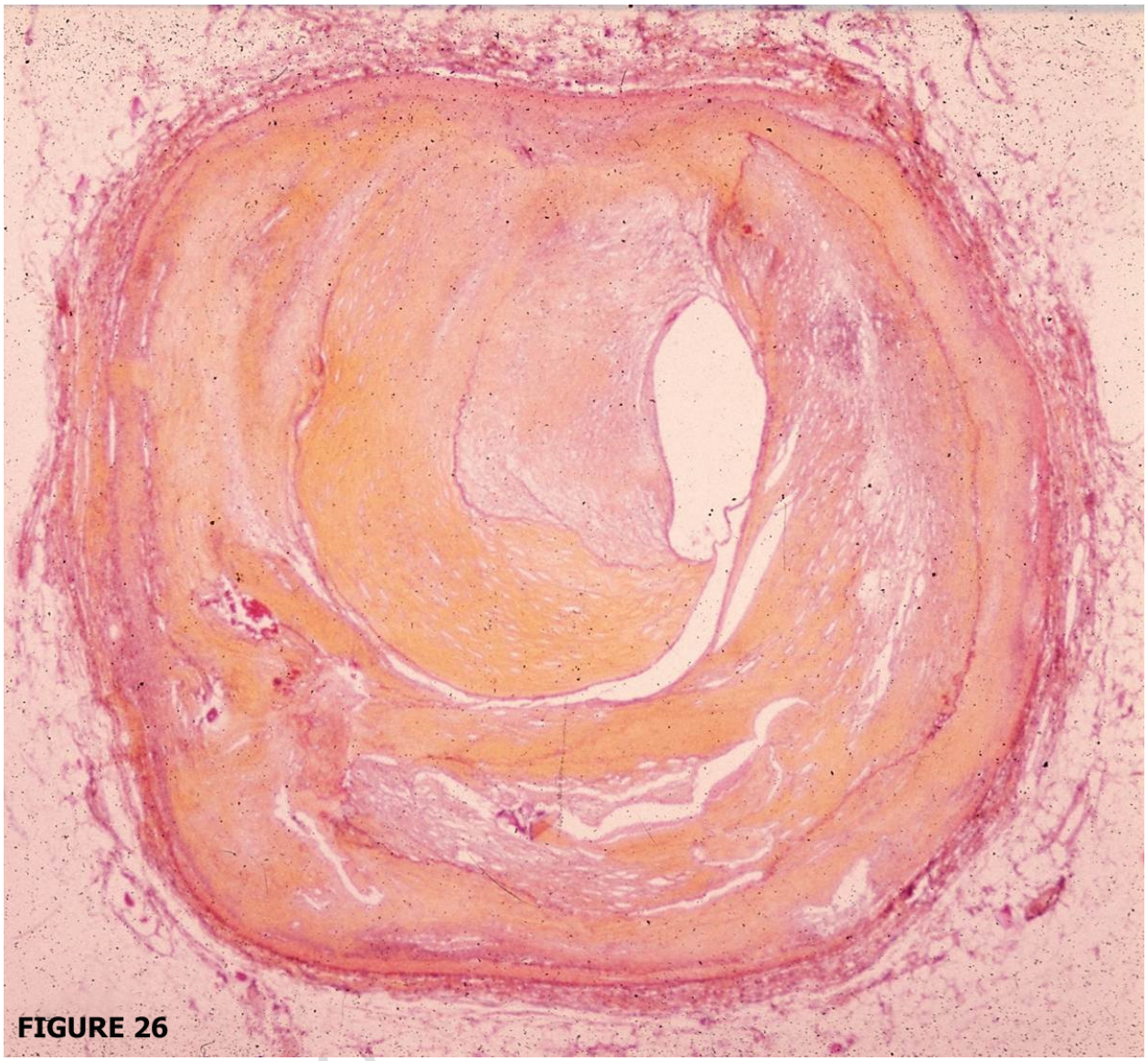

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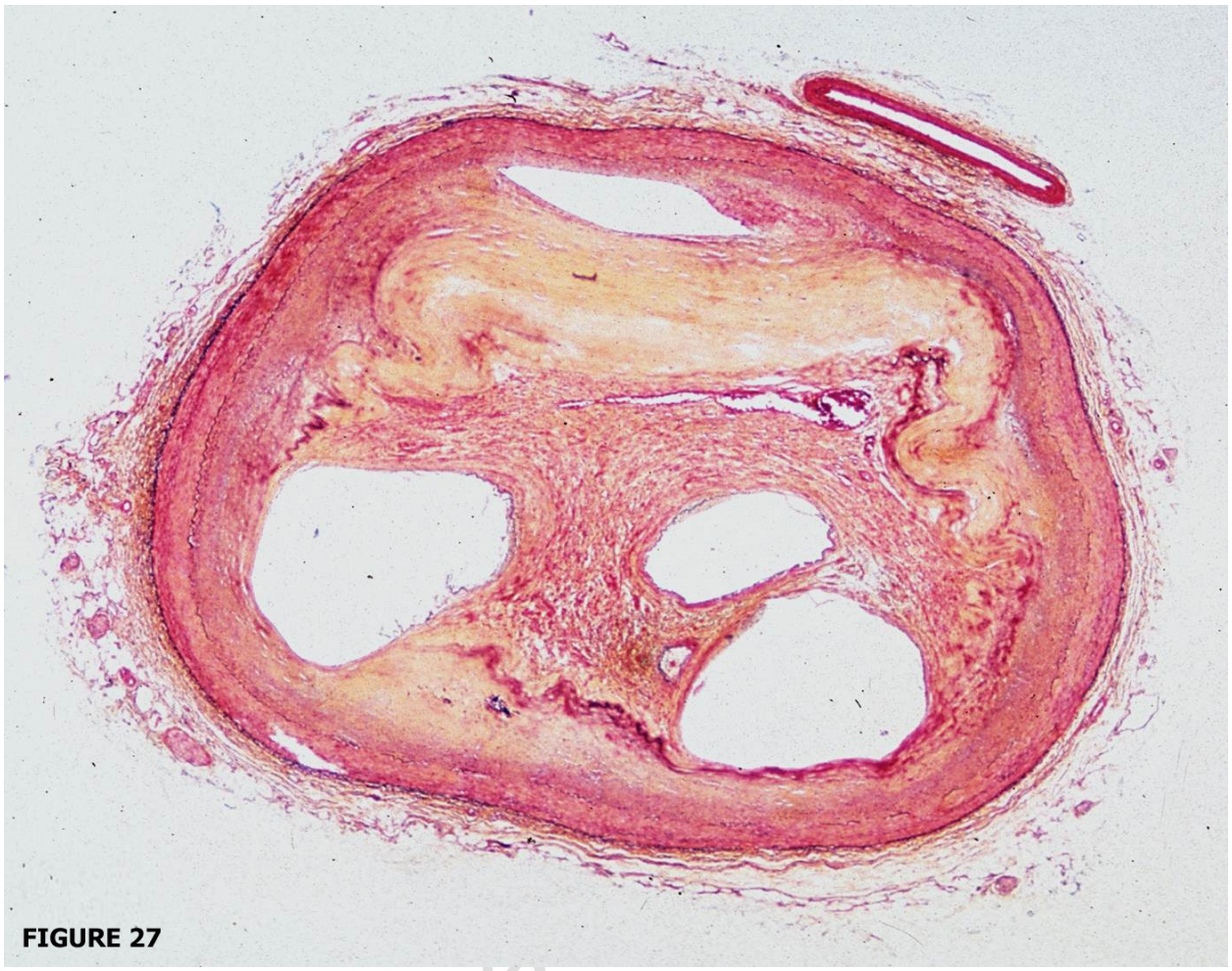

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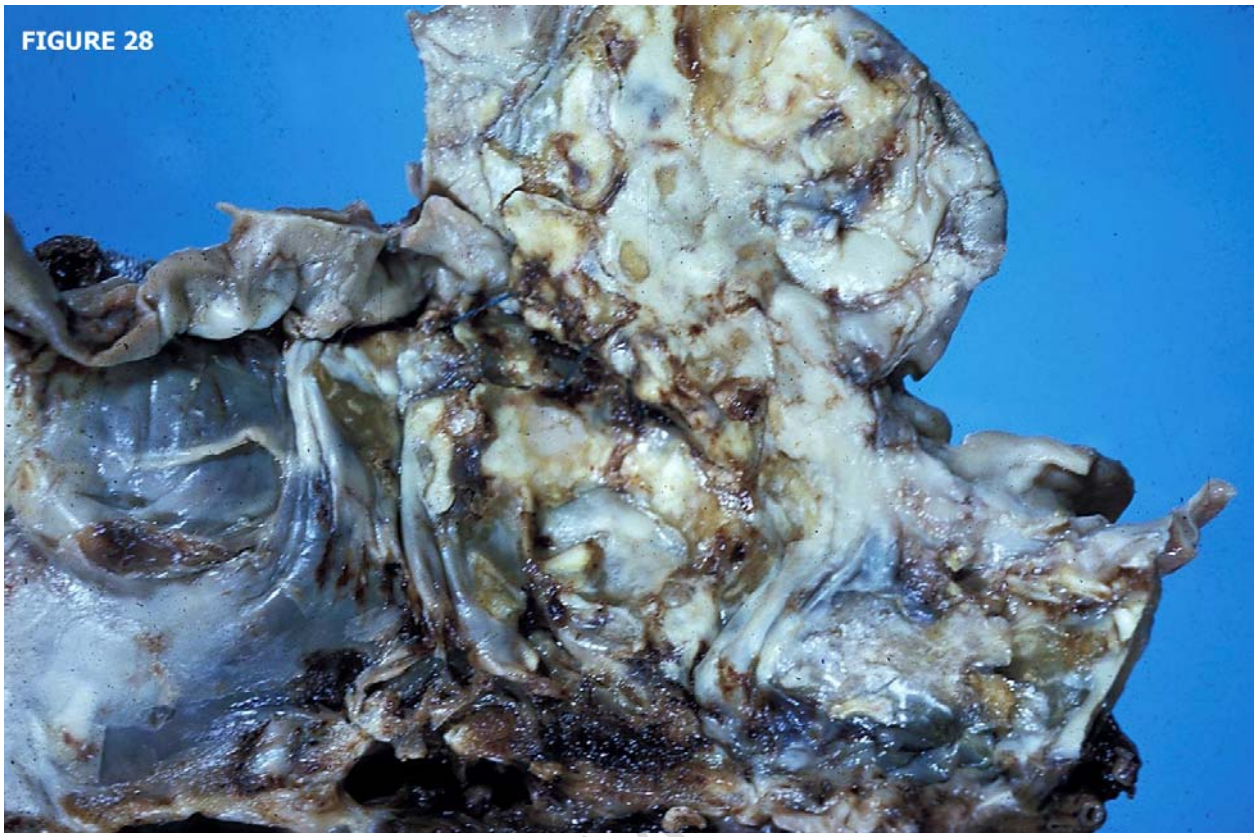

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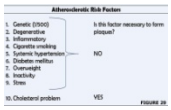

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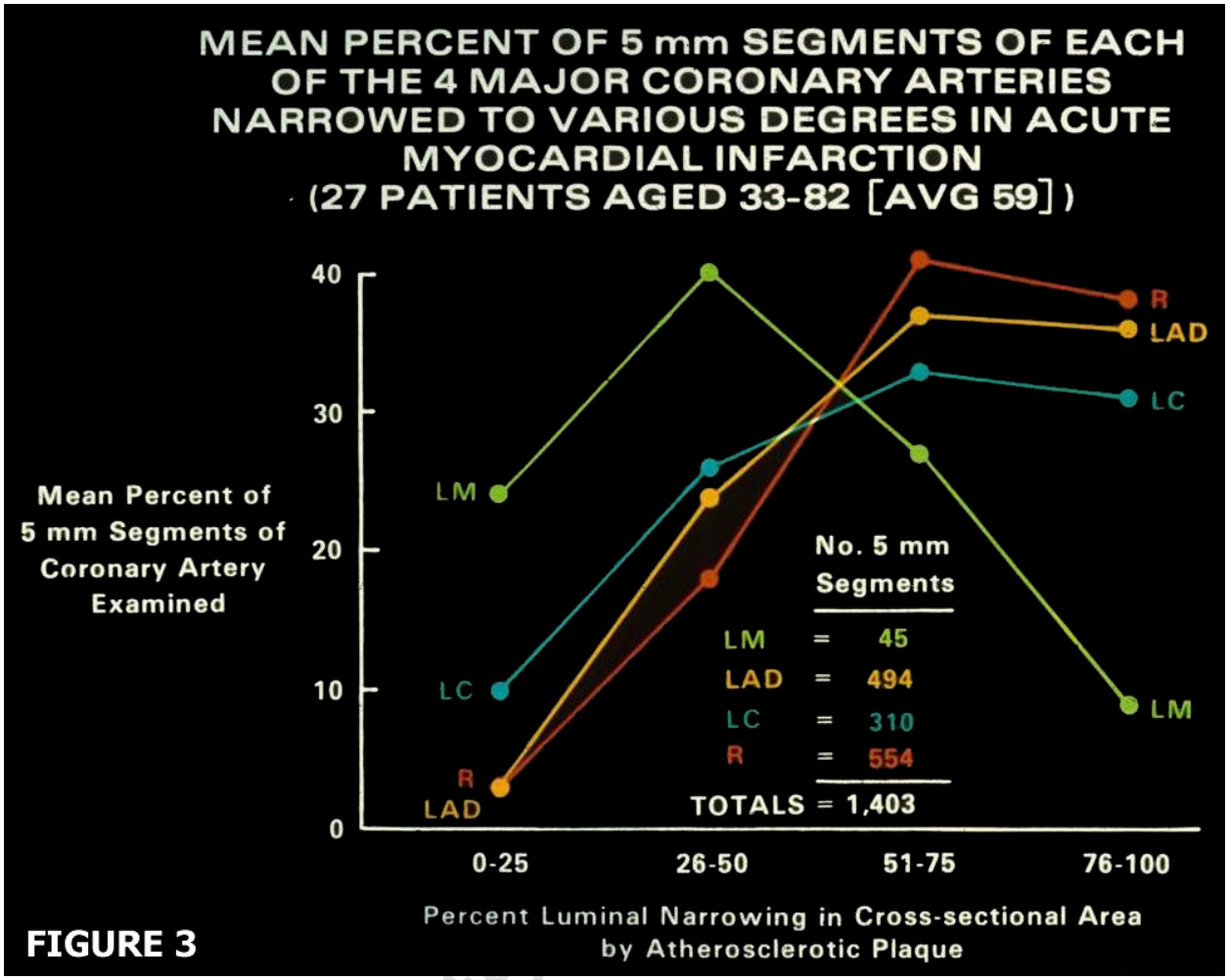

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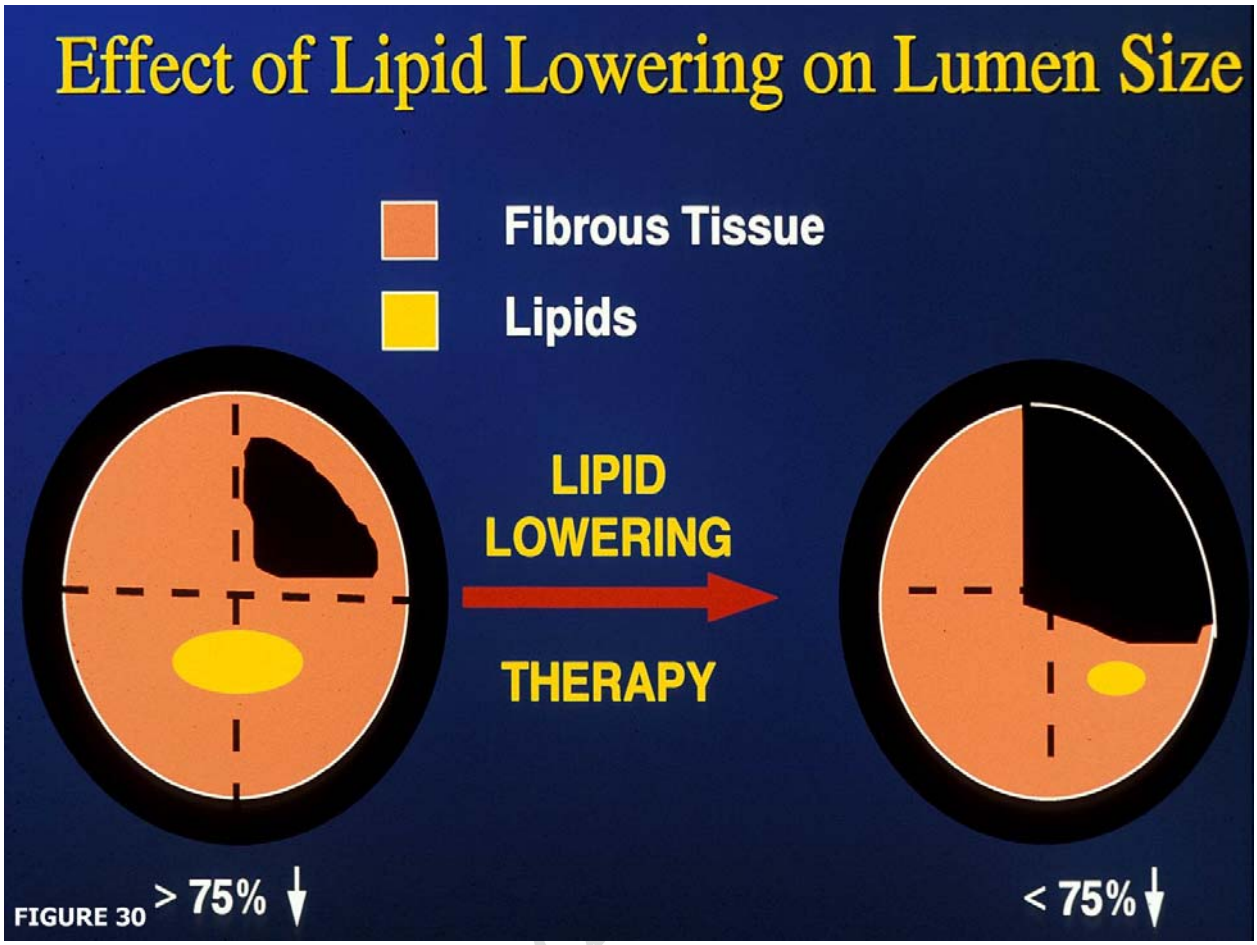

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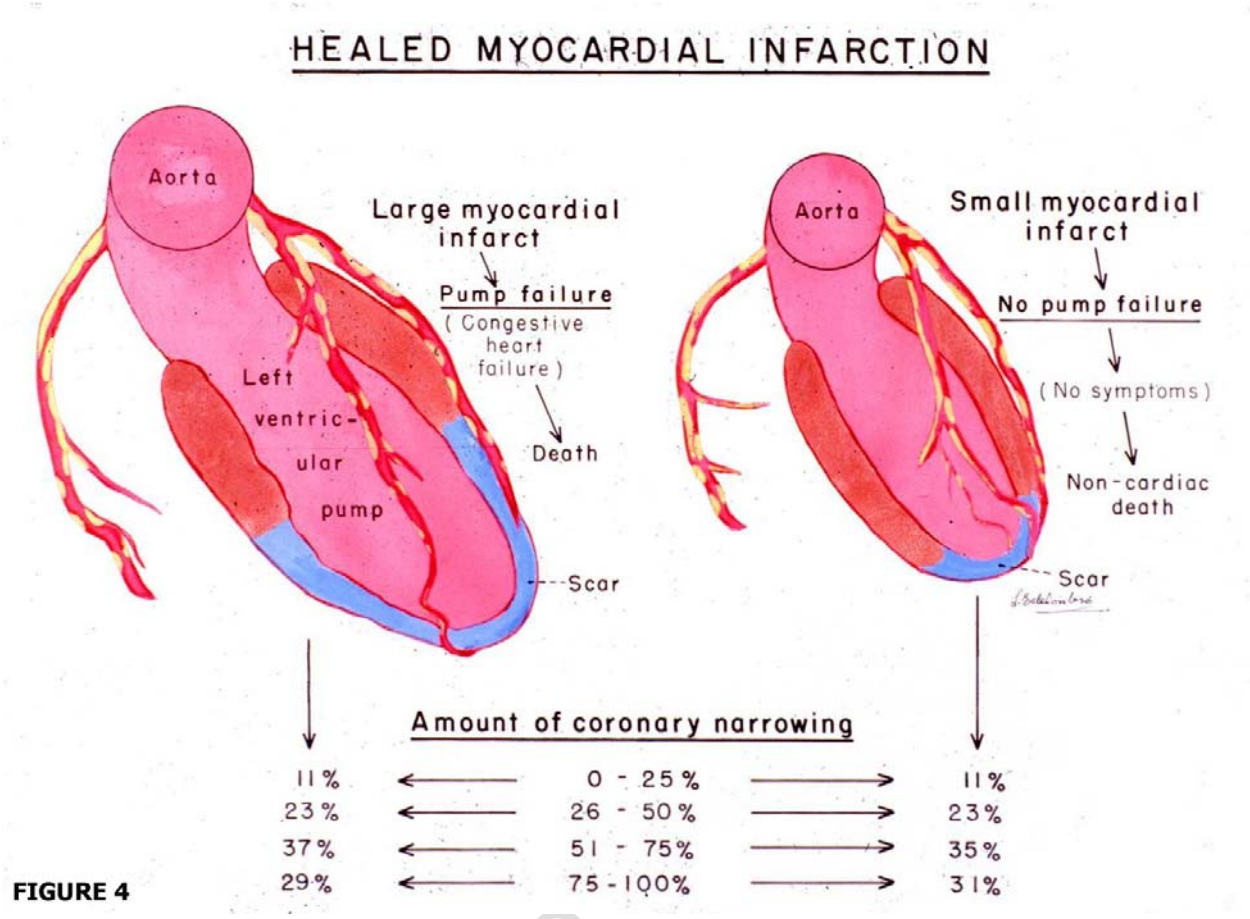

FIGURE 4

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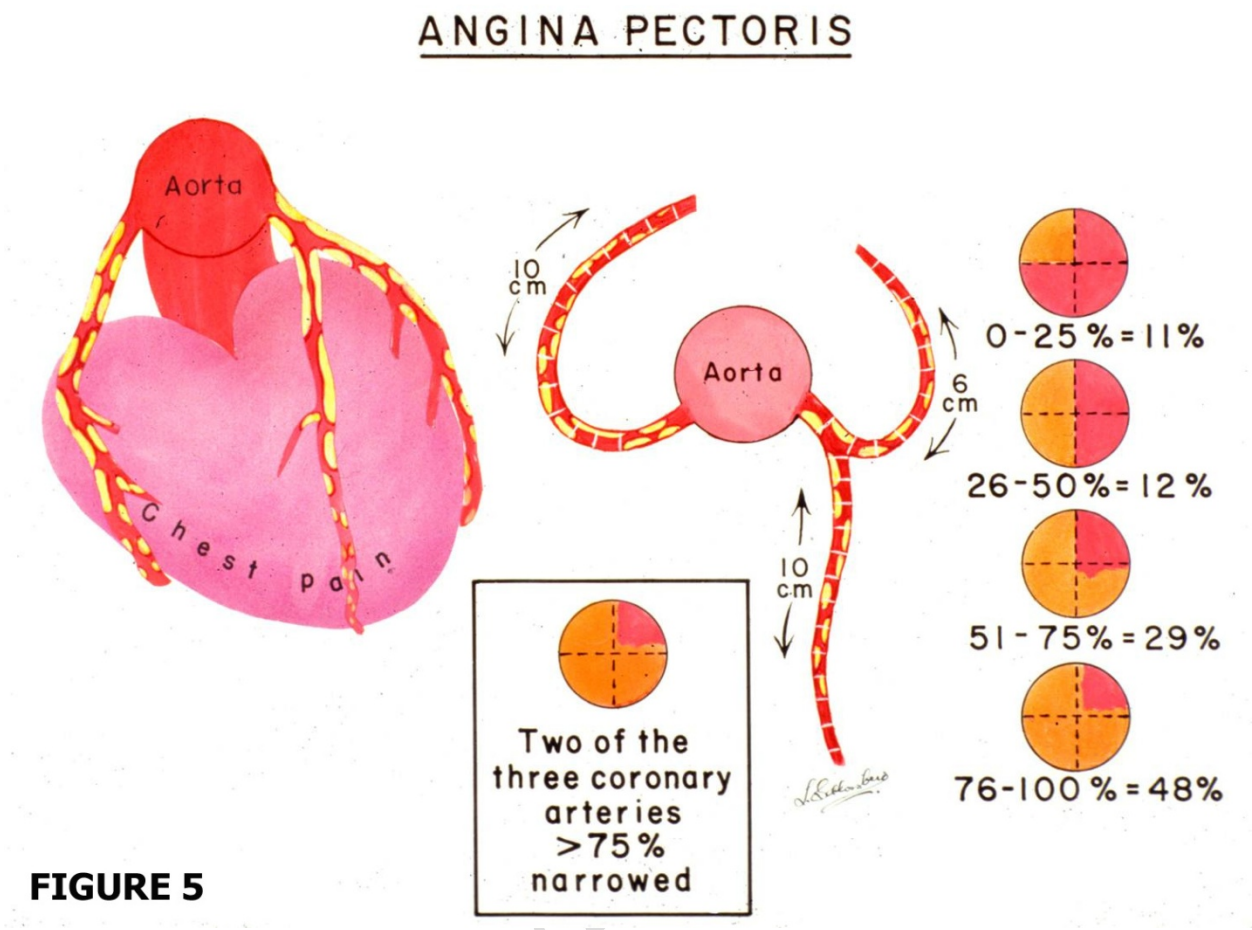

FIGURE 5

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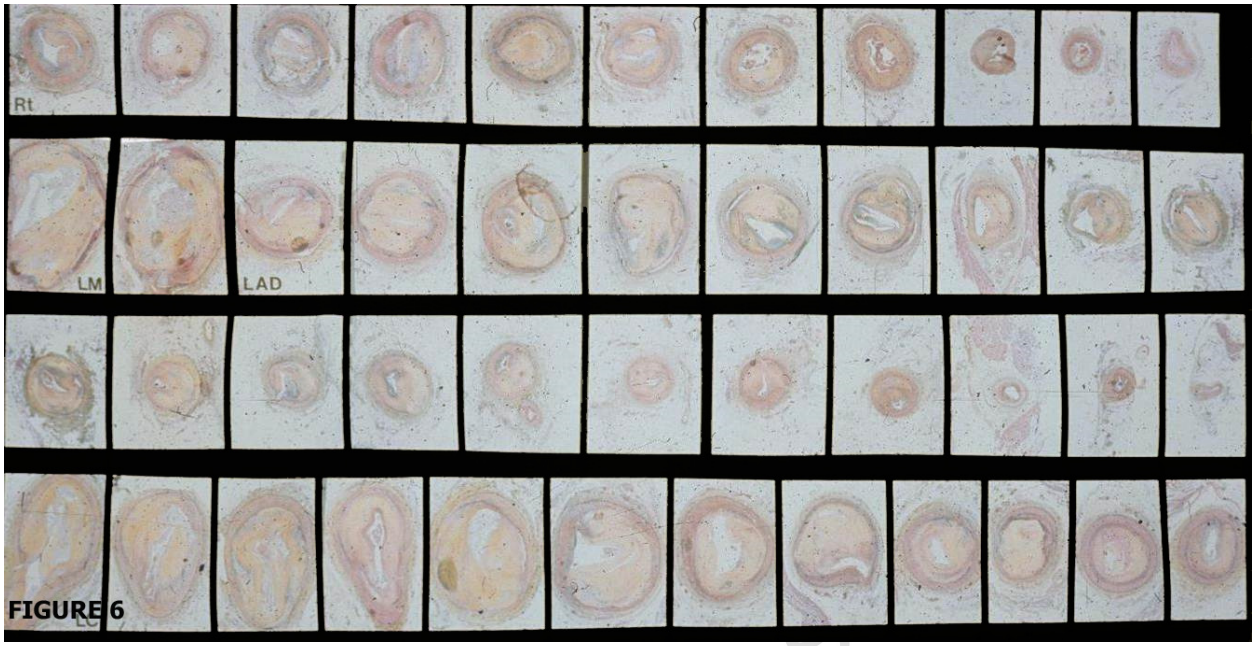

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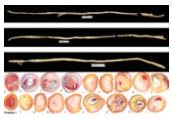

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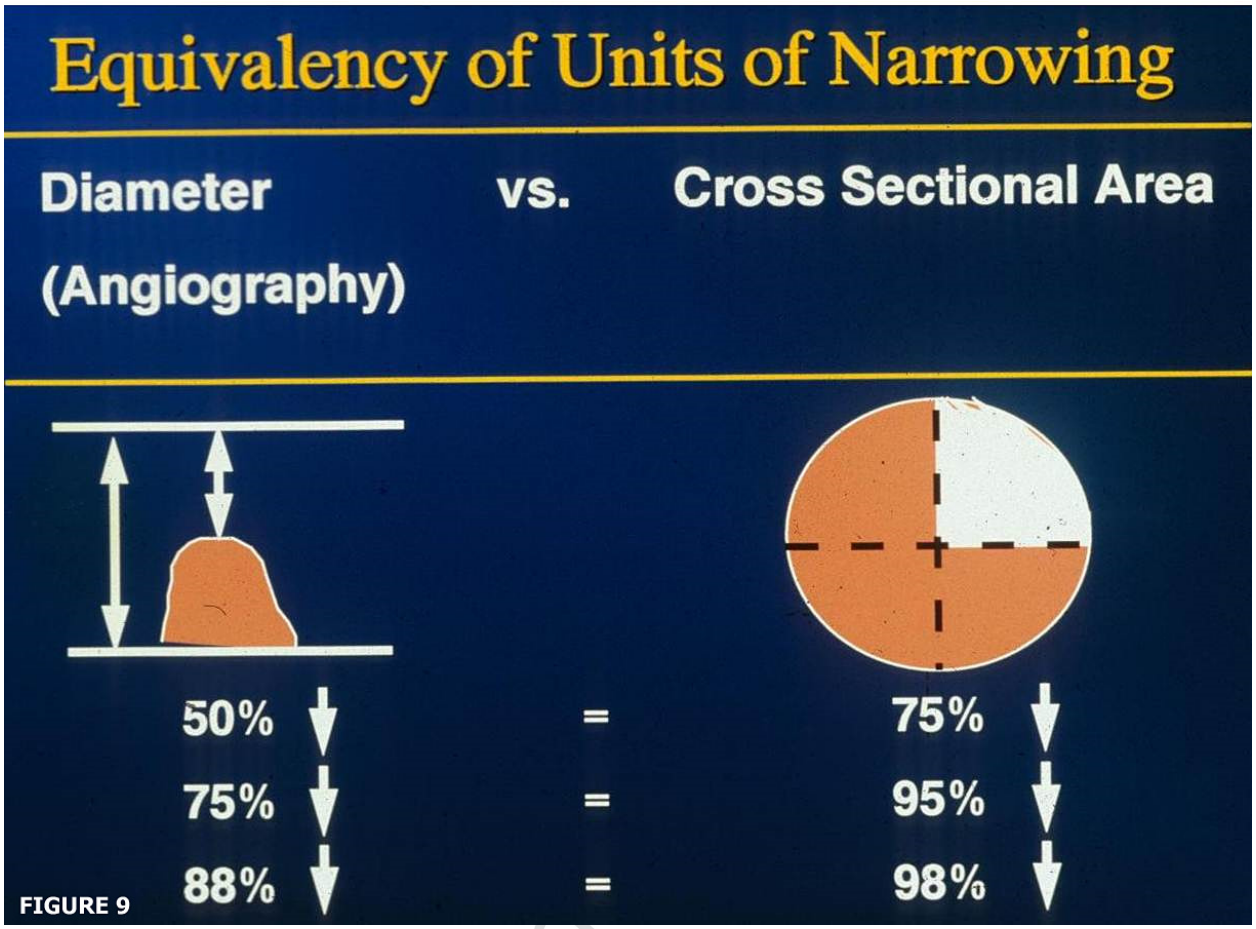

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