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Antibiotics for Myocardial Infarction?

A Possible Role of Infection in Atherogenesis and Acute Coronary Syndromes

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Abstract

The role of inflammatory mechanisms in the initiation, progression and clinical expression of atherosclerosis is increasingly appreciated. With this awareness, the possibility that acute or chronic infection may initiate or modulate these processes is an active area of investigation.

Infectious organisms may influence the atherosclerotic process through direct local effects on the coronary endothelium, on vascular smooth muscle cells and on macrophages in the atherosclerotic lesion. Infection may also exert systemic effects by inducing the elaboration of cytokines, the creation of a hypercoagulable state and by activating monocytes, causing possible transmission of infectious material to atherosclerotic lesions. Macrophages may then elaborate multiple mediators which destabilise plaque, promoting rupture and progression.

Seroepidemiological data have identified associations between clinically active atherosclerosis and evidence of infection with *Helicobacter pylori*, *Chlamydia pneumoniae* and some herpesviridae. In addition, pathological examinations have demonstrated the presence of infectious organisms in coronary artery plaques. Cytomegalovirus, for example, has been identified pathologically to be associated with transplant vasculopathy and with an increased risk of restenosis following coronary intervention. Finally, recent pilot trials have demonstrated that macrolide antibacterial treatment directed against *C. pneumoniae* reduces the risk of recurrent coronary events.

Infectious organisms may therefore influence atherogenesis through multiple pathways, and pathological and seroepidemiological investigations provide evidence of this association. Future large-scale clinical trials are needed to further evaluate the evidence of causality and the efficacy of antibacterial therapy for coronary artery disease.

The concept that infection may cause atherosclerosis was first proposed almost a century ago by Osler and Ophuls,[1] among others.[2] This was suggested by simple pathological inspection of the atherosclerotic lesion, which was noted to have a cellular infiltrate of macrophages or foam cells. In 1978, Fabricant et al.[3] showed that chickens infected with an avian herpes virus developed arterial lesions pathologically similar to those of atherosclerosis. Since that time, cardiovascular research has advanced our understanding of atherosclerosis in the areas of thrombosis, lipid metabolism, systemic diseases and inflammation. Concurrently with these advances, research in other fields has demonstrated how chronic and perhaps acute infectious processes may contribute to the development

of previously deemed 'noninfectious' diseases. Chronic infection with *Helicobacter pylori*, for example, may cause ulcer disease and gastric cancer. In addition, viral infections have been associated with lymphoproliferative disorders, cervical cancer and perhaps multiple myeloma. The convergence of these fields may be upon us as provocative recent work prompts us to reconsider notions first proposed a century ago.[4,5]

In order to evaluate whether infections with particular bacterial and viral organisms play a role in atherosclerosis and myocardial infarction, it is first prudent to review our current understanding of the atherosclerotic mechanism. Then we can ask whether it is conceptually plausible that infections may influence this system. Finally, observational and some interventional data can be assessed.

1. Outline of Atherosclerosis

In the progression of coronary atherosclerosis, 8 morphologically different lesions have been defined (fig. 1) which may be found in various phases of clinical disease (fig. 2). Low density lipoprotein (LDL) cholesterol has been implicated in the earliest stages of atherosclerosis. Spontaneous atherogenesis is thought to be initiated with the passage of LDL cholesterol through dysfunctional vascular endothelium at sites of low shear stress. Endothelial dysfunction is primarily caused by a disturbance

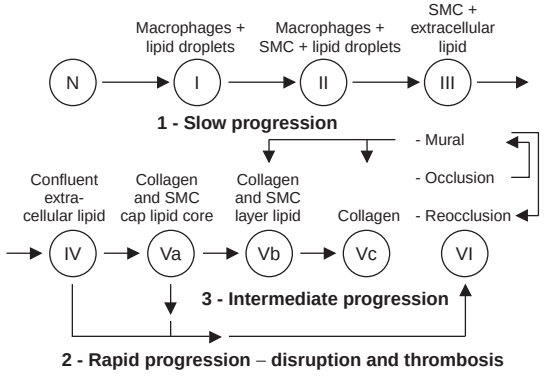

Fig. 1. Schematic representation of lesion morphology and histopathology in coronary atherosclerosis (reproduced from Fuster,[6] with permission). **SMC** = smooth muscle cells.

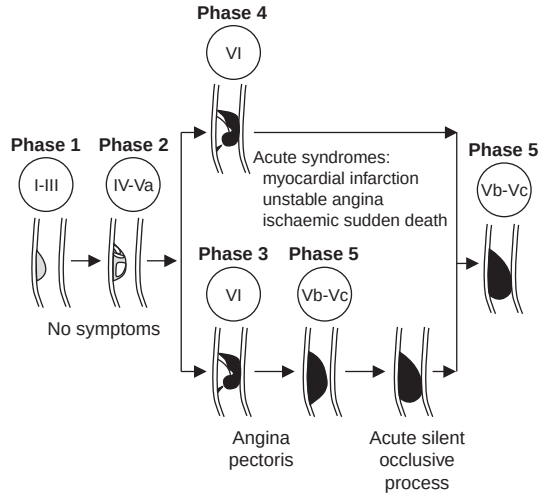

Fig. 2. Atherosclerotic lesions in humans. Staging of phases and lesion morphology in the clinical progression of coronary atherosclerosis according to histopathological and clinical studies (reproduced from Fuster,[6] with permission). **SMC** = smooth muscle cells.

in the normal laminar blood flow in certain parts of the coronary tree such as at branch points or bends.[7]

In addition to mechanical stresses, however, many other systemic and local factors may cause dysfunction of the normally anti-atherogenic endothelium (table I).[8] All of these factors, however, are part of or in turn trigger an inflammatory response in the vessel wall. Multiple cell types can mediate this process, including monocyte-derived macrophages and specific T lymphocyte subsets; granulocytes are rarely involved.

The transformed endothelium allows passage of LDL cholesterol and expresses multiple adhesion molecules for platelets and inflammatory cells. LDL cholesterol that penetrates the vascular endothelium undergoes partial oxidation. Oxidised LDL cholesterol, in turn, causes further endothelial dysfunction. In addition, monocytes that penetrate the vascular endothelium differentiate into macrophages that take up oxidised LDL cholesterol, which activates macrophages and may be a potent chemoattractant. The resulting 'foam cells,' or lipid-laden macrophages, accumulate in the athero-

sclerotic lesion and ultimately may rupture, releasing oxidised LDL cholesterol and cytotoxic enzymes.[9,10] These inflammatory mediators trigger a fibroproliferative response from vascular smooth muscle cells. These are the initial steps in the creation of a visible, lipid-rich atherosclerotic plaque.[11]

2. Plaque Disruption and Thrombosis

The atherosclerotic lesions that develop as a result of these processes do not necessarily give rise to clinical events. Disruptions of a vulnerable or unstable plaque (type IV and Va lesions in fig. 1) with a subsequent change in plaque geometry and thrombosis (type VI) may result in acute occlusion or sub-occlusion with clinical manifestations of acute coronary syndromes.[12,13]

2.1 Plaque Disruption and Inflammation

Plaque disruption probably results from both 'active' and 'passive' properties of the lesion. Vulnerable plaques tend to be relatively small, but soft or vulnerable to 'passive' disruption because of the high lipid content. In addition, a better understanding of the 'active' phenomena of plaque disruption is evolving which appears tightly linked to the inflammatory response. Thus, atherectomy specimens obtained from patients with acute coronary syndromes reveal high macrophage-rich areas. Activated macrophages are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and a family of matrix metalloproteinases (collagenases, gelatinases and stromelysins) that may weaken the fibrous cap, predisposing it to rupture.[14,15]

Table I. Clinical situations associated with localised or systemic endothelial dysfunction (adapted from Drexler[8])

Hypertension
Diabetes mellitus
Smoking
Hypercholesterolaemia
Endotoxaemia/sepsis/lipopolysaccharide
Oxidative stress
Congestive heart failure
Transplant vasculopathy
Thrombosis

2.2 Thrombosis and Macrophages

Different plaque types exhibit different degrees of thrombogenicity. The lipid core, abundant in cholesterol ester, for example, appears to be the most thrombogenic. Tissue factor, a small glycoprotein which initiates the extrinsic clotting cascade, has been localised in the lipid core of symptomatic plaques and is associated with macrophage-rich areas. The extent of thrombosis, which affects clinical expression, is no doubt modulated by factors intrinsic and extrinsic to the plaque (table II).[14,15] In addition to plaque composition, local dysfunction of the endothelium transforms its normally antithrombotic phenotype by impairing release of nitric oxide and prostacyclin, 2 potent vasodilators with antiplatelet activity, as well as altering surface expression of fibrinolytic and antithrombotic glycoproteins. The elaboration of inflammatory mediators (cytokines) and growth factors establishes a critical cross-talk between the major cell types in the inflamed atherosclerotic plaque. For example, macrophage products may induce vascular smooth muscle cell apoptosis and endothelial dysfunction. Finally, systemic factors also influence the extent and frequency of plaque rupture and alter the thrombogenic response.[14,16]

Most episodes of plaque disruption are not clinically apparent but rather expand lesions, incorporating thrombus and greater inflammatory infiltrates.[9] When superimposed thrombus on a ruptured atherosclerotic plaque interferes with coronary flow, an acute coronary syndrome occurs. In some patients, such as those with unstable angina, the thrombus formation may be transient and produce chest pain lasting only 10 to 20 minutes. In non–Q-wave myocardial infarction, probably due to more extensive vessel and plaque disruption, flow limitation is more severe and persistent. In Q-wave infarction, coronary flow is completely suspended for more than 1 hour, resulting in transmural cellular necrosis.

Table II. Local and systemic thrombogenic risk factors for acute plaque thrombosis

Local factors
Degree of plaque disruption
Degree of stenosis
Plaque composition (e.g. lipid-rich plaque, tissue factor)
Surface of residual thrombus
Vasoconstriction
Systemic factors
Catecholamines (e.g. smoking, stress, cocaine exposure)
Cholesterol, lipoprotein(a), homocysteinaemia, hypertension, diabetes mellitus
Fibrinogen, impaired fibrinolysis (e.g. plasminogen activator inhibitor-1)
Inflammatory mediators (e.g. cytokines)

3. Potential Role of Infections

Within this framework, infection can modulate a systemic inflammatory reaction, making plaque development and rupture more likely, and may also influence the environment of the plaque itself (see fig. 3).

3.1 Potential Direct Effects of Infectious Organisms on Plaque Components

Endothelial dysfunction, the proposed starting point for atherosclerosis, can be induced by systemic or local infection. Bacterial endotoxin and tumour necrosis factor-α (TNFα), for example, inhibit endothelial-dependent generation of nitric oxide.[17] Even a brief exposure to endotoxin in healthy volunteers produces long-lasting local endothelial dysfunction, a process termed 'endothelial stunning'.[18] Herpesviridae, including cytomegalovirus, have been shown to infect human vascular wall cells, including vascular smooth muscle cells and endothelial cells. Direct virus infection of endothelial cells has been shown to alter their antithrombotic phenotype and may spur recruitment of inflammatory cells.[19] Vascular smooth muscle, when infected by certain viruses, may alter expression of growth-controlling proteins (see section 4.1). Finally, monocytes may be infected with viruses or bacteria and harbour and possibly deliver them to inflamed plaques. Infected monocytes may also become activated by infectious organisms or by neighbouring T lymphocytes.[4,20]

3.2 Potential Indirect Effects of Infectious Organisms

The potential roles of systemic inflammatory responses have been highlighted recently. In the Physician's Health Study, elevated levels of C-reactive protein, a nonspecific marker of systemic inflammation, were a strong independent predictor of subsequent cardiovascular events.[21] In addition, the protective benefit of aspirin (acetylsalicylic acid) was concentrated among those with elevated levels of C-reactive protein, suggesting that aspirin's anti-inflammatory properties may be important.

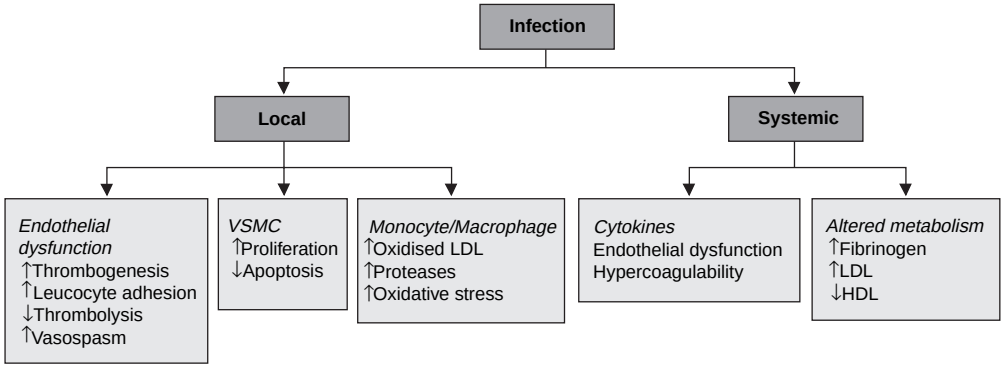

Fig. 3. Potential local and systemic effects of infection on atherosclerosis. **HDL** = high density lipoprotein cholesterol; **LDL** = low density lipoprotein cholesterol; **VSMC** = vascular smooth muscle cell; ↑ = increased; ↓ = decreased.

Levels of several cytokines have been found to be elevated during acute coronary syndromes.[22] Circulating cytokines may modulate endothelial function, promoting thrombosis, and activate macrophages, causing the elaboration of toxic free radicals and degradative enzymes.

Systemic infection may also directly modulate other cardiovascular risk factors. Fibrinogen levels, a known risk factor for cardiovascular disease, are known to increase during infection and to exhibit seasonal variations which mirror periods of respiratory infections as well as increases in cardiovascular disease.[23] In addition, acute infection may lower levels of high density lipoprotein and elevate levels of triglycerides.[24]

4. Evidence Supporting the Aetiological Role of Specific Organisms

4.1 Cytomegalovirus and Other Herpesviridae

Cytomegalovirus is a common β-herpes virus. It may cause an infectious mononucleosis–like syndrome and hepatitis in otherwise healthy hosts, but is a common pathogen responsible for aggressive pulmonary and disseminated diseases in the immunocompromised. Most adults are seropositive for cytomegalovirus and presumably harbour virus in a latent state for life, as with other herpesviridae. However, several epidemiological studies have demonstrated an association between elevated cytomegalovirus antibody titres and the presence of atherosclerosis.[25]

Cytomegalovirus seropositivity has been correlated with the advanced development of vasculopathy (a process similar to atherosclerosis) in multiple studies of cardiac transplant patients.[26] In one study, patients who developed clinical cytomegalovirus infection had a 30% risk of developing vascular lesions 6 years following transplantation, compared with less than 10% in the absence of infection (infection was defined by a 4-fold rise in anti-cytomegalovirus IgG antibody titre).[26] A recent study performed in rats with heterotopic cardiac allografts demonstrated that treatment with ganciclovir significantly reduced intimal thickening in the presence of cytomegalovirus infection.[27]

Based on pathological data demonstrating cytomegalovirus DNA sequences and viral inclusions in restenotic and atherosclerotic lesions, investigators prospectively studied 75 consecutive patients undergoing directional coronary atherectomy for coronary disease.[28] Patients who were seropositive for cytomegalovirus prior to the procedure had a greater than 5-fold increased rate of restenosis (43% versus 8%, $p = 0.002$). Increased titre also predicted restenosis. No patient demonstrated acute infection in that all tests for anti-cytomegalovirus IgM antibodies were negative.

A potential mechanism by which cytomegalovirus virus may affect atherosclerosis and restenosis hinges on the monocyte. Latent cytomegalovirus may reside in the vessel wall and intermittently replicate. Alternatively, cytomegalovirus integrated into mononuclear cell precursor DNA may cause circulating monocytes to be a vector delivering virus to sites of vessel inflammation.[29] Macrophages have been demonstrated to be a similar source of circulating HIV in patients with AIDS.[30] In a provocative study, Guetta et al.[29] demonstrated that endothelial cells, smooth muscle cells and oxidised LDL cholesterol can all activate cytomegalovirus viral replication in infected monocytes. These macrophages were also shown to be able in turn to infect endothelial cells and vascular smooth muscle cells with cytomegalovirus. Cytomegalovirus-infected smooth muscle cells may then obtain a growth advantage, perhaps contributing to proliferative responses in atherosclerosis and restenosis, which may in part be linked to cytomegalovirus-induced changes in expression of the regulatory protein p53.[31]

4.2 *Helicobacter pylori*

Epidemiological similarities between peptic ulcer and coronary artery disease has prompted several studies showing links between *H. pylori* infection and atherosclerosis. *H. pylori* is a Gram-negative rod which is closely associated with the gastric mucosa and has been strongly implicated in the

development of peptic ulceration, as well as gastric carcinoma and low-grade B cell lymphomas of the gastrointestinal tract. It appears that *H. pylori* infection is largely acquired in childhood and exhibits marked ethnic and socioeconomic diversity.

It is particularly appealing to study *H. pylori* in coronary artery disease because chronic infection can be easily treated. An association of *H. pylori* infection with coronary disease was suggested by a case-control study by Mendall et al.,[32] in which seropositivity for *H. pylori* conferred a 2-fold increased risk of coronary artery disease among almost 200 Caucasian white men, after controlling for conventional risk factors and socioeconomic status. Another study supported this association and additionally found that elevated serum fibrinogen levels and total leucocyte count were found more often in those seropositive for *H. pylori*.[33]

It is, of course, difficult to control for the multiple possible confounding factors and biases which weaken any case-control design. For example, *H. pylori* infection in childhood is linked with socioeconomic status and overcrowding.[34] A Finnish case-control study, for example, failed to demonstrate a statistically significant relationship for coronary artery disease risk but rather found higher serum triglyceride levels in those who were seropositive for *H. pylori*.[35] Another study found that after controlling for cigarette smoking, hypertension, blood glucose and some socioeconomic variables, any significant association disappeared.[36] It seems that, although chronic infection with *H. pylori* would be an appealing contributing factor to coronary artery disease since it is easily treatable, it is more likely that previous studies have been misleading due to extensive confounders. A recent larger prospective study, which thereby minimised the effects of both random error and socioeconomic and other biases, found no relation between *H. pylori* infection and ischaemic heart disease.[34] A meta-analysis of 18 epidemiological studies involving over 10 000 patients supports the lack of a significant association.[37]

4.3 *Chlamydia pneumoniae*

Chlamydia pneumoniae, a highly prevalent Gram-negative bacterium capable of causing respiratory disease, is an obligate intracellular pathogen and may survive within macrophages for years.[5,38] *C. pneumoniae* DNA has been detected in coronary atherectomy specimens from atherosclerotic lesions.[39] In a prospective study in Utah, immunofluorescent antibodies detected chlamydial antigen in 79% of 90 atherectomy specimens from atherosclerotic lesions but in fewer than 5% of 24 non-atherosclerotic samples.[40] In a recent case report, live organism has been isolated and grown from a human atherosclerotic lesion.[41]

However, the relationship between bacterial DNA or antigens and live organisms and whether they may play an active or 'bystander' role remains unclear. In a rabbit model, 2 recent studies have demonstrated that intranasal inoculation with *C. pneumoniae* triggered the development of early and intermediate atherosclerotic lesions.[42,43] In another study using the cholesterol-fed rabbit, intranasal inoculation with *C. pneumoniae* resulted in increased intimal thickness in the aorta as well as significant increases in indices of plaque area. Treatment with azithromycin significantly mitigated these effects of *C. pneumoniae*.[44]

Several seroepidemiological studies have examined possible associations of *Chlamydia* with human cardiovascular disease, with variable results.[2,45-47] In a population-based case-control study, elevated IgG antibodies to *C. pneumoniae* were associated with an odds ratio of 2.6 for the presence of at least 1 vessel with angiographically obstructive coronary artery disease.[2] On further analysis, this association was limited to current cigarette smokers. Other studies have demonstrated increased risk of coronary artery disease among those seropositive for prior *C. pneumoniae* infection, but again only among certain geographical or medical subsets.[46,48]

Epidemiological studies, however, are prone to multiple sources of error. It may be possible that *C. pneumoniae* infection may be more likely among those at risk for coronary disease based on some

other poorly controlled risk factor and may be confounded by socioeconomic status and ethnicity. Alternatively, illness due to these infectious organisms may make those with otherwise clinically unapparent coronary artery disease seek medical assistance. Or, there may be a true causal relationship which may be too weak to detect in higher risk individuals because of the small size of these studies. Finally, most sero-epidemiological studies have not distinguished between acute, chronic or recurrent infections.

Two recent trials have examined the efficacy of antibiotic therapy against *C. pneumoniae* in acute coronary syndromes. In a British trial, 220 patients attending an outpatient clinic more than 6 months after a myocardial infarction were screened for serum IgG antibodies against *C. pneumoniae*.[49] Patients with clinical infection were excluded, as were 7 patients who had sera which cross-reacted with other *Chlamydia* species. Patients with high titres which persisted at 3 months were treated in a placebo-controlled double-blind manner with azithromycin 500 mg/day for 3 or 6 days. Azithromycin is a macrolide (azalide) antibiotic that achieves high tissue concentrations, has a long half-life and has a broad spectrum of action including activity against *Chlamydia* species and other intracellular pathogens. Cardiovascular events, defined as hospitalisation for an acute coronary syndrome or revascularisation procedure or cardiovascular death, were monitored for 18 months from the original clinic visit. In an analysis pooling the placebo group with those with low antibody titres and combining both treatment durations with azithromycin, participants with high titres were at greater risk for subsequent events and antibiotic treatment eliminated this excess risk (table III). These results persisted after controlling for traditional cardiovascular risk factors and paralleled changes in biochemical markers of hypercoaguability and macrophage activation. The benefit of treatment was not limited to those whose antibody level decreased, which may suggest an effect independent of eliminating *C. pneumoniae* infection. This may be related to protective effects against other infections or to another property of azithromycin.

The ROXIS (roxithromycin in non–Q-wave coronary syndromes) pilot study examined the effect of roxithromycin, also a macrolide antibiotic, in a double-blind placebo-controlled manner among patients with unstable angina and non–Q-wave myocardial infarction.[50] Roxithromycin 150mg twice daily was given for up to 30 days to 102 of 202 randomised patients. The combined end-point included severe recurrent ischaemia, acute myocardial infarction, or cardiac death. During the first 72 hours, 9 patients from the roxithromycin group and 7 from the placebo group suffered clinical events and were excluded from the final analysis. A statistically significant reduction in the triple end-point was observed among patients who completed 72 hours of treatment: among those treated with placebo, there were 9 events (10% of patients) versus only 1 event (1% of patients) in those re-

Table III. Effect of azithromycin therapy in survivors of myocardial infarction with high titres of antibody against *Chlamydia pneumoniae* (adapted from Gupta et al.,[49] with permission)

Group	Total cardiovascular events [n (%)]	Odds ratio compared with seronegative group (95% confidence interval)	
		unadjusted	adjusted[a]
Seronegative (n = 59)	4 (7)		
Low-titre seropositive (n = 74)	11 (15)	2.4 (0.7-8)	2.0 (0.6-6.8)
High-titre seropositive: no treatment (n = 40)[b]	11 (28)	5.2 (1.5-17.8)[c]	4.2 (1.2-15.5)[c]
High-titre seropositive: azithromycin treatment (n = 40)	3 (8)	1.1 (0.2-5.3)	0.9 (0.2-4.6)

a Controlled for age, diabetes mellitus, smoking, hypertension, hyperlipidaemia and previous coronary revascularisation.

b Includes patients assigned to placebo and also a group who were not recruited into the intervention study.

c $p < 0.05$ compared with the seronegative group.

n = number of patients.

Table IV. Evidence supporting the aetiological role of infectious agents in atherosclerosis (adapted from Libby et al.[4])

	Cytomegalovirus/other herpesviridae	*Helicobacter pylori*	*Chlamydia pneumoniae*
Seroepidemiology			
atherosclerosis	+/–	±	+
restenosis	+/–	–	–
transplantation atherosclerosis	+/–	–	–
Pathogen present in atheroma	+/±	–	+
Produces atheroma in animals	+/+	–	+
Evidence for causality	–/–	–	+

+ = good evidence; ± = equivocal evidence; – = no evidence.

ceiving roxithromycin ($p < 0.05$). The longer term efficacy of these interventions was recently questioned and publication of the final results is awaited.[51] Again, it is difficult to separate antibiotic effects specific for *C. pneumoniae* from actions against other bacteria, or from possible anti-inflammatory properties. Doxycycline, for example, has been shown to prevent the structural breakdown of elastin in rat aortic tissue.[52]

5. Conclusions

The critical steps in the generation, progression, and ultimate clinical presentation of atherosclerotic lesions are all intimately involved with systemic and local inflammatory and reparative processes. Although many potential triggers and risk factors have been elucidated, it certainly seems plausible that chronic or acute infections may play important roles (see table IV). Basic investigations have identified multiple points in which systemic or local infectious processes may intervene. Epidemiological data, although intriguing, are limited and cannot distinguish whether infectious agents are innocent bystanders without pathological importance or if they are suitable targets for specific therapy. As research into the inflammatory nature of acute and chronic cardiovascular diseases progresses, we await large-scale trials of antibiotics to determine whether they have a role in mollifying the triggers of plaque progression and rupture.

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