Predisposition to Atherosclerosis by Infections
Role of Endothelial Dysfunction

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**Background**—Several microorganisms have been implicated in the pathogenesis of atherosclerosis. We hypothesized that infections may predispose to atherosclerosis by inflicting endothelial injury.

**Methods and Results**—Of 375 patients undergoing coronary angiography, 218 had assessment of endothelial function using intracoronary acetylcholine (ACH) and of endothelium-independent function with sodium nitroprusside and adenosine. Immunoglobulin-G antibody titers to cytomegalovirus, *Chlamydia pneumoniae*, *Helicobacter pylori*, hepatitis A virus, and herpes simplex virus-1 were measured. Pathogen burden was defined as the number of positive antibodies. Although positive serology to individual pathogens tended to be associated with increased incidence of coronary arteriosclerosis (CAD), the pathogen burden correlated with the presence of CAD, even after adjustment for risk factors (OR 1.3; 95% CI, 1.05 to 1.6, *P*=0.018). Moreover, the severity of CAD was independently associated with the pathogen burden (*P*=0.001). Pathogen burden was an independent predictor of endothelial dysfunction, determined as the percent change in coronary vascular resistance in response to ACH (*P*=0.009) but not the responses to sodium nitroprusside or adenosine. Pathogen burden was also an independent determinant of endothelial function in the subgroup with angiographically normal coronary arteries.

**Conclusions**—The immunoglobulin-G antibody response to multiple pathogens (pathogen burden) is an independent risk factor for endothelial dysfunction and the presence and severity of CAD. Endothelial dysfunction provides the crucial link by which pathogen may contribute to atherogenesis. (Circulation. 2002;106:184-190.)

**Key Words:** atherosclerosis, infection, viruses, endothelium, coronary disease

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Many patients with coronary atherosclerosis (CAD) lack conventional risk factors, suggesting that there are additional unidentified factors that contribute to vascular injury. Epidemiological studies indicate that infectious agents may predispose to atherosclerosis and its adverse clinical events. Organisms implicated are intracellular pathogens, including viruses such as cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), and hepatitis A virus (HAV) and bacteria such as *Chlamydia pneumoniae* and *Helicobacter pylori.* Because some pathogens have been identified in atherosclerotic plaques, it has been hypothesized that they may precipitate vascular inflammation by either persistent infection or by immune-mediated injury.

Endothelial dysfunction is one of the earliest manifestations of atherosclerosis, and it is noteworthy that certain pathogens can infect endothelial cells and increase synthesis of tissue factor, cell-surface thrombin expression, platelet adherence, and expression of adhesion molecules, cytokines, and growth factors and decrease prostacyclin release. Based on these observations and our preliminary findings that the risk of CAD correlates not only with the presence of individual infections (as determined by seropositivity) but more strongly with the aggregate number of infections (pathogen burden), we hypothesized that infection with multiple pathogens may contribute to human CAD by inflicting endothelial cell injury. In this investigation, we determined whether there is a relationship between the pathogen burden and severity of CAD and hypothesized that such a predisposition may be secondary to coronary vascular endothelial dysfunction.

**Methods**

**Patients**

We studied 375 patients with either CAD defined as angiographic presence of plaquing or more severe disease or angiographically smooth, normal coronary arteries (NCAs) undergoing diagnostic cardiac catheterization. Preliminary experience from a smaller cohort of 233 patients has been previously reported, and this study examines for the first time the relation between pathogen burden and disease severity and endothelial function. Disease severity was scored as 0 for those with smooth normal epicardial coronary arteries, 0.5 for...
TABLE 1. Characteristics of All Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>0–1</th>
<th>2–3</th>
<th>4–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>375</td>
<td>43</td>
<td>167</td>
<td>165</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>227 (61)</td>
<td>27 (63)</td>
<td>93 (56)</td>
<td>107 (65)</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±1</td>
<td>51±2</td>
<td>55±1</td>
<td>60±1†</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>211±3</td>
<td>204±7</td>
<td>209±4</td>
<td>214±4</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>131±6</td>
<td>131±6</td>
<td>133±4</td>
<td>142±3</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>44±1</td>
<td>45±2</td>
<td>46±2</td>
<td>42±†</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>192 (51)</td>
<td>16 (37)</td>
<td>85 (51)</td>
<td>91 (55)*</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>40 (19)</td>
<td>6 (14)</td>
<td>31 (19)</td>
<td>38 (23)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>215 (57)</td>
<td>21 (49)</td>
<td>98 (59)</td>
<td>96 (58)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.87±0.03</td>
<td>0.74±0.08</td>
<td>0.87±0.05</td>
<td>0.90±0.05</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>246 (60)</td>
<td>19 (44)</td>
<td>101 (60)</td>
<td>126 (76)*</td>
</tr>
</tbody>
</table>

†P<0.05 compared with patients with 0 or 1 infection; †P<0.05 compared with 2 to 3 infections.

Results expressed as percent or mean±SEM.

Plaquing (<50% severity), and 1, 2, or 3 for those with single-,
double-, or triple-vessel epicardial coronary stenosis of >50%, respectively.

Of the 375 patients, 218 underwent measurement of vascular function. Inclusion criteria included presence of at least 1 unobstructed coronary artery (or bypassed artery). Patients with multivessel disease, recent myocardial infarction, or severe valvular heart disease were excluded. Cardiac medications were withdrawn for at least 48 hours. The protocol was approved by the Institutional Review Board of the National Heart, Lung and Blood Institute, and informed written consent was obtained.

Vascular Function Studies

A 6-French guide catheter was introduced into an unobstructed (<30% stenosis) coronary artery, and coronary blood flow (CBF) velocity was measured using a 0.014- or 0.018-inch Doppler flow wire (Cardiometrics Flowire, Endosonics Corp). Endothelium-dependent vasodilation was estimated by measuring CBF and epicardial responses to an infusion of intracoronary acetylene (ACH) at a rate of 30 μg/min for 2 minutes to obtain an estimated 10−6 mol/L intracoronary concentration. Endothelium-independent function was estimated with intracoronary sodium nitroprusside (SNP) (40 μg/min) infusion for 3 minutes and coronary flow reserve with adenosine infused at 2.2 mg/min for 2 minutes. When drugs were infused into a single coronary artery, the infusion rate was halved.

CBF was derived from the CBF velocity and diameter measurements using the formula (π×average peak velocity×0.125×diameter). Coronary vascular resistance (CVR) was calculated as mean arterial pressure divided by CBF. For calculating CBF, diameter was measured in a 0.25- to 0.5-cm segment of vessel beginning 0.25 cm beyond the tip of the flow wire. Quantitative angiography was performed with the ARTREK software (Quantim 2001, Statview, ImageComm Systems, Inc) or PIE medical CAAS system. Additionally, mid and distal segments of the epicardial coronary arteries were also measured after each intervention.

Serum IgG Antibodies to CMV, HSV-1, HAV, C pneumoniae, and H pylori

Serum samples obtained from all study subjects were frozen at −80°C. Enzyme-linked immunosorbent assay kits were used to determine serum immunoglobulin-G (IgG) antibodies to CMV (Wampole, Cranbury, NJ) and H pylori (Meridian Diagnostics, Cincinnati, Ohio), respectively. Serum IgG antibodies for HAV (Abbott HAVAB EIA, Abbott Park, Ill) and HSV-1 (American Medical Laboratories, Inc, Chantilly, Va) were determined using an enzyme immunoassay. Serum IgG and IgA (n=228) antibodies for C pneumoniae were assayed using a microimmunofluorescence test (University of Washington). Seropositivity was determined according to manufacturer’s instructions, as described before. The prevalence of IgG antibodies in the general population (age >50 years) has been reported as follows: 40% to 100% for CMV, 60% to 100% for HSV1, 50% to 100% for HAV, 70% to 95% for C pneumoniae, and >40% for H pylori based on socioeconomic class. Serum CRP was measured by fluorescence polarization immunoassay technology (TDxPLEx analyzer, Abbott Labs).

Statistical Analysis

Data are expressed as mean±SEM. Differences between means were compared by paired or unpaired Student’s t test, as appropriate. All probability values are 2-tailed, and a value <0.05 was considered statistically significant. Univariate correlations were performed using the Pearson’s correlation coefficient. Multivariate analyses included the use of stepwise regression and the General Linear Models procedure in SAS to identify significant relationships. This procedure was used to test whether the presence of CAD, the severity of CAD (0-, 1-, 2-, or 3-vessel disease) in the total population, or percent change in CVR with ACH (in patients undergoing vascular function studies) were related to age, sex, body mass index, hypertension (blood pressure >140/90 mm Hg), diabetes, cigarette use, history of hypercholesterolemia (cholesterol level >240 mg/dL or on lipid-lowering therapy), CRP level, antibody status to each of the 5 pathogens, or the total number of infections (pathogen burden).

Results

Patient characteristics are summarized in Table 1. The prevalence of IgG antibodies directed against the 5 microorganisms was as follows: CMV, 64%; HSV-1, 83%; HAV, 52%; C pneumoniae, 76%; and H pylori, 42%. Thus, 11.5% had previous exposure to 0 or 1 pathogen, 44.5% to 2 or 3 pathogens, and 44% to 4 or 5 pathogens. Among conventional risk factors, univariate correlates of CAD prevalence were age (P<0.0001), male sex (P<0.0001), hypercholesterolemia (P<0.0001), hypertension (P=0.01), diabetes (P<0.0001), and smoking (P<0.0001). After multivariate adjustment, age (OR 1.09), male gender (OR 3.6), hypercholesterolemia (OR 4.1), smoking (OR 3.4), and diabetes (OR 5.1) remained independent predictors of CAD prevalence (all P<0.001).
CAD Prevalence and Seropositivity to Individual Pathogens

The frequency of past infection with each organism was higher in patients with CAD compared with those with NCA, with the difference being statistically significant in those with seropositivity for CMV, HAV, and *H pylori* after univariate analysis (Table 2). After adjustment for conventional risk factors, both CMV and HAV remained significant predictors of CAD. When additionally adjusted for CAD risk factors and presence or absence of all individual infections, only HAV remained independently predictive of CAD (Table 2). The prevalence of CAD in patients seropositive and seronegative for IgA antibody against *C pneumoniae* (n=228) was similar (67.1% versus 60.8%, *P*=NS, respectively).

**Pathogen Burden and Severity of CAD**

The severity of CAD was also related to pathogen burden; the prevalence of multivessel disease (2- and 3-vessel disease) was significantly higher in patients with greater pathogen burden (*P*=0.001) (Figure 1). Pathogen burden remained an independent predictor of the severity of CAD after multivariate adjustment for conventional risk factors and CRP level (*P*=0.029).

**Interaction With CRP**

The CRP level was higher in patients with CAD (0.92±0.04 versus 0.72±0.06, *P*=0.03). After adjustment for conventional risk factors, a high CRP level (>0.5 mg/dL) remained an independent predictor of CAD (Table 2). There was also a correlation between pathogen burden and CRP levels (*r*=0.1, *P*=0.04), with a higher CRP level in patients with a greater pathogen burden (Table 1). To investigate whether the pathogen burden was an independent determinant of the

### Table 2. Association Between Individual Pathogens, CRP, and the Presence of CAD

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Frequency of Positive Antibodies (%)</th>
<th>Adjusted* OR 95% CI</th>
<th>Frequency of Positive Antibodies (%)</th>
<th>Adjusted* OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>No CAD: 53.4, CAD: 68.7</td>
<td>1.4 (0.8–2.8)</td>
<td>No CAD: 53.4, CAD: 68.7</td>
<td>1.4 (0.8–2.8)</td>
</tr>
<tr>
<td>HAV</td>
<td>No CAD: 35.7, CAD: 60.2</td>
<td>2.6 (1.4–5)</td>
<td>No CAD: 35.7, CAD: 60.2</td>
<td>2.6 (1.4–5)</td>
</tr>
<tr>
<td><em>C pneumoniae</em></td>
<td>No CAD: 71.3, CAD: 78</td>
<td>1.1 (0.6–2.2)</td>
<td>No CAD: 71.3, CAD: 78</td>
<td>1.1 (0.6–2.2)</td>
</tr>
<tr>
<td>HAV-1</td>
<td>No CAD: 79, CAD: 85.8</td>
<td>1.0 (0.5–2.1)</td>
<td>No CAD: 79, CAD: 85.8</td>
<td>1.0 (0.5–2.1)</td>
</tr>
<tr>
<td><em>H pylori</em></td>
<td>No CAD: 34.4, CAD: 46.7</td>
<td>0.6 (0.3–1.2)</td>
<td>No CAD: 34.4, CAD: 46.7</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td>CRP&gt;0.5 mg/dL</td>
<td>No CAD: 59.7, CAD: 78</td>
<td>2.6 (1.3–5.2)</td>
<td>No CAD: 59.7, CAD: 78</td>
<td>2.6 (1.3–5.2)</td>
</tr>
</tbody>
</table>

*Adjusted for conventional risk factors and individual pathogens.

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**Figure 1.** Top, Relation between pathogen seropositivity and the percent prevalence of no, mild (plaquing or 1-vessel disease), or multivessel (2- or 3-vessel) CAD. Linear trend overall achieves significance at *P*<0.001. Bottom, Adjusted OR for presence of CAD (adjusted for presence of hypertension, hypercholesterolemia, diabetes, smoking status, age, and sex) (95% CI for 2 or 3 infections, 1.0 to 3.8; 4 to 5 infections, 2.0 to 8.3).
presence of CAD, a multivariate analysis was repeated adjusting for conventional risk factors and CRP level. This demonstrated that both pathogen burden (OR 1.27, \( P = 0.036 \)) and high CRP level (OR 2.7, \( P = 0.004 \)) were independent predictors of CAD, together with the conventional risk factors described above (Figure 2).

### Individual Pathogens and Vascular Function

The coronary vasodilator response to ACH was used as an index of endothelial function, and the responses to adenosine and SNP were used as indices of endothelium-independent function.\(^{20}\)

Microvascular and epicardial dilation with ACH tended to be lower in subjects seropositive to any 1 of the pathogens compared with seronegative patients (Table 3), reaching statistical significance for patients seropositive for \( H \) pylori \( (P = 0.002) \), HAV \( (P = 0.03) \), and HSV1 \( (P = 0.03) \) for the microcirculation and for HSV1 \( (P = 0.02) \) for the epicardial circulation. No differences in the vasomotor responses to SNP or adenosine were observed between seropositive and seronegative patients (Table 3).

### Pathogen Burden and Endothelial Function

**Microcirculation**

There was a significant correlation between pathogen burden and the percent increase in flow \( (P = 0.01) \) or the percent decrease in CVR with ACH \( (P = 0.009) \) (Figure 3). Thus, compared with patients with antibodies to \( \geq 1 \) pathogen, \( ACH \)-mediated microvascular dilation was diminished in patients seropositive to \( \geq 4 \) pathogens \( (\sim 50 \pm 4\% \text{ versus } \sim 40 \pm 3\% \text{ decrease in CVR}) \) (Figure 3). The pathogen burden \( (P = 0.009) \) and hypertension \( (P = 0.014) \) were both predictors of the percent change in CVR with \( ACH \), independent of risk factors, presence or absence of atherosclerosis, or CRP level.

Because the prevalence of CAD was higher in patients with a greater pathogen burden (Table 1), and because atherosclerosis is known to be associated with endothelial dysfunction, we examined this relationship in patients with NCA. Progressive impairment of \( ACH \)-dependent microvascular dilation was also observed with increasing numbers of infections in the subgroup of 86 patients with NCA (Figure 4), and the pathogen burden was in independent predictor of the percent change CVR after multivariate analysis \( (P = 0.03) \).

Serum CRP levels did not correlate with the \( ACH \) response. Multivariate adjustment for CRP levels did not alter the correlation between pathogen burden and endothelial function.

**Epicardial Circulation**

Patients with a higher pathogen burden \( (\geq 4 \text{ past infections}) \) had a constrictor response with \( ACH \), consistent with greater endothelial dysfunction compared with those with a lower pathogen burden \( (\leq 3 \text{ infections}) \) in all patients \( (\sim 2.7 \pm 1.2\% \text{ versus } 0.6 \pm 1.2\%, P = 0.05, \text{ respectively}) \) and in the subset with NCA \( (\sim 3.5 \pm 2\% \text{ versus } 2.2 \pm 1.4\%, P = 0.02) \).

**Pathogen Burden and Responses to SNP and Adenosine**

Vasodilation in response to SNP did not correlate with pathogen burden \( (P = 0.9) \) (Figure 3). Similarly, there was no difference in SNP-mediated epicardial dilation in those with low \( (\leq 3 \text{ infections}) \) compared with high-pathogen burden \( (\geq 4 \text{ past infections}) \) \( (18 \pm 2\% \text{ and } 16 \pm 2\%, P = 0.3) \). Furthermore, flow reserve with adenosine was also similar in the 3 pathogen subsets \( (P = 0.6, \text{ Figure 3}) \) in all patients and those with NCA (Figure 4).

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### TABLE 3. Coronary Microvascular and Epicardial Responses to ACH and SNP According to Seropositivity to Individual Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>ACH (%)</th>
<th>SNP (%)</th>
<th>Adenosine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑ Flow</td>
<td>↓ CVR</td>
<td>ΔED</td>
</tr>
<tr>
<td>CMV positive</td>
<td>96±8 ± 38±2</td>
<td>-1.8±1</td>
<td>112±7</td>
</tr>
<tr>
<td>CMV negative</td>
<td>108±15</td>
<td>43±3</td>
<td>-0.7±2</td>
</tr>
<tr>
<td>HSV-1 positive</td>
<td>93±7</td>
<td>38±2*</td>
<td>-2.4±1</td>
</tr>
<tr>
<td>HSV-1 negative</td>
<td>129±16</td>
<td>47±3</td>
<td>2.5±2*</td>
</tr>
<tr>
<td>HAV positive</td>
<td>91±10</td>
<td>37±3</td>
<td>-2.6±1</td>
</tr>
<tr>
<td>HAV negative</td>
<td>114±9</td>
<td>43±3</td>
<td>-0.3±2</td>
</tr>
<tr>
<td>C pneumoniae positive</td>
<td>100±8</td>
<td>39±2</td>
<td>-0.9±1</td>
</tr>
<tr>
<td>C pneumoniae negative</td>
<td>103±11</td>
<td>43±4</td>
<td>-2.3±2</td>
</tr>
<tr>
<td>H pylori positive</td>
<td>78±8 pattern</td>
<td>34±3†</td>
<td>-2.2±1</td>
</tr>
<tr>
<td>H pylori negative</td>
<td>117±9</td>
<td>45±2</td>
<td>-0.5±1</td>
</tr>
</tbody>
</table>

*ED indicates epicardial diameter. \( *P \leq 0.05; \) †P < 0.005.
Discussion

Increasing seroepidemiologic and mechanistic evidence suggests that infectious agents are implicated in the genesis of atherosclerosis.\textsuperscript{1–10,15–19} The present investigation importantly extends the evidence that infections and, particularly, pathogen burden contribute to atherogenesis. Sixty-nine percent of our patients were infected by \geq 3 of the common pathogens studied; most importantly, the pathogen burden was an independent risk factor for the presence of CAD, the severity of CAD, and coronary vascular endothelial dysfunction. The odds of having CAD were 4.1-fold higher in patients with 4 or 5 previous infections compared with those with 0 or 1 previous infection. This confirms our previous findings and extends these observations by illustrating that the severity of CAD was related to the pathogen burden.\textsuperscript{7} There was a progressive decline in the dilator response to ACH as pathogen burden increased, providing a mechanistic explanation of how infections might predispose to atherogenesis by causing endothelial dysfunction. Together with conventional risk factors, pathogen burden imposed an additional independent risk for the presence and severity of CAD and of endothelial dysfunction.

Increasing pathogen burden was also associated with a higher CRP level, indicating an increased systemic inflammatory response, and, as observed previously, a higher CRP level was an independent predictor of CAD. Combined together, these findings raise the intriguing possibility that the aggregate effect of multiple pathogens is to precipitate endothelial dysfunction and inflammation, both processes that predispose to atherosclerosis.

Many studies have demonstrated associations between seropositivity to individual pathogens and atherosclerosis.\textsuperscript{1–10,21} Importantly, we found that the pathogen burden predicted the presence and severity of CAD more strongly than any single pathogen, and recent studies examining multiple infections have confirmed our observations.\textsuperscript{22–25} Nevertheless, other investigations have failed to demonstrate such associations,\textsuperscript{26–30} a disparity that may be because analysis was limited to single pathogens, because of the use of cardiac events as end points, or because the negative studies have been performed in relatively healthy populations.\textsuperscript{28–30}

Our study suggests that the composite effect of multiple pathogens, rather than any single organism, is the development of endothelial dysfunction. The fact that endothelium-

![Figure 3. Effects of pathogen burden on the changes in coronary blood flow and coronary vascular resistance in response to ACH, SNP, and adenosine in all patients. *P<0.02, **P<0.01.](http://circ.ahajournals.org/)

![Figure 4. Effects of pathogen burden on the changes in coronary blood flow and coronary vascular resistance in response to ACH, SNP, and adenosine in patients with normal coronary arteries. *P<0.05, **P<0.01.](http://circ.ahajournals.org/)
independent responses were preserved in all patient subsets indicates that the impairment of the endothelial layer does not affect smooth muscle function. Importantly, pathogen burden correlated with endothelial function even in those with NCA. It seems that endothelial dysfunction may be one of the underlying mechanisms by which multiple intracellular pathogens may actually contribute to the earliest processes leading to the development of atherosclerosis and to its more rapid progression to multivessel disease.

Endothelial dysfunction unequivocally predisposes to atherosclerosis, and patients with atherosclerosis and its risk factors exhibit both microvascular and epicardial coronary vascular endothelial dysfunction.20,31,32 Studies now demonstrate more rapid progression to adverse atherosclerotic events in individuals with endothelial dysfunction and also in those with multiple past infections.22,24,25,33 Our observation that pathogen burden is an independent determinant of endothelial dysfunction additionally strengthens the epidemiologic, mechanistic, and prognostic link between infection with multiple pathogens and atherosclerosis.

It is likely that despite major differences in the biologic and clinical consequences that result from human infection with these pathogens, there may be shared pathways by which diverse organisms produce vascular endothelial injury. These pathways and, as demonstrated in this study, also lead to an integrated injury of the vascular endothelium and inflammation.13,14

Limitations

This is a cross-sectional investigation that establishes an association between pathogen burden and endothelial dysfunction but not causality. Thus, increasing pathogen burden may not be the direct cause of the endothelial dysfunction or atherosclerosis, but merely a surrogate marker of some other presently undiscovered risk factor. Thus, the conclusions of this study must be regarded as preliminary and hypothesis-generating. In addition, we considered a positive IgG antibody titer against these pathogens as evidence of past infection. It is not known whether seropositivity indicates recent, past, or reactivated latent infection or whether it represents reinfection.

Conclusions

The number of positive IgG antibody responses to multiple pathogens (pathogen burden) is an independent risk factor for the presence and severity of CAD and of endothelial dysfunction in a population of patients undergoing coronary angiography. As such, the study provides a crucial link by which pathogens may contribute to atherogenesis.25,34,35

Acknowledgments

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References


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