Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet

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ABSTRACT We studied the effect of propranolol on the diet-induced coronary artery atherosclerosis (CAA) in 30 adult male cynomolgus monkeys living in social groupings of five animals each. Animals in the “treated” segment (n = 15) consumed propranolol, which was mixed into an atherogenic diet. Animals in the “untreated” group (n = 15) consumed only the atherogenic diet. Finally, the social groupings were subjected to disruption through monthly redistribution of monkeys among the groups within each treatment segment. The experiment lasted 26 months, following which all animals underwent autopsy during which the coronary arteries were evaluated for atherosclerosis. Regarding atherosclerosis, we observed a significant interaction between social status and experimental condition (p < .03). Socially dominant animals had (as in previous studies) significantly exacerbated CAA, but only in the untreated segment; the effect of social dominance on CAA was abolished by long-term administration of propranolol. The antiatherogenic effect of propranolol on dominant animals was independent of the influences of serum lipid concentrations, blood pressure, and resting heart rate. We conclude that treatment with β-adrenergic-blocking agents may confer a degree of protection against CAA among individuals behaviorally predisposed to coronary heart disease.

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THERE IS increasing evidence that the behavioral attributes of individuals contribute to risk for atherosclerosis and coronary heart disease (CHD). Among human beings, the so-called type A behavior pattern (and, more specifically, the propensity to experience excessive anger or hostility) has been found to be predictive of CHD events in prospective studies of initially healthy individuals.1-7 Similarly, we have observed that when male cynomolgus monkeys fed atherogenic diets are housed in an unstable or stressful social setting, the highly aggressive and competitive dominant animals develop greater coronary artery atherosclerosis than their more submissive, subordinate counterparts.8,9 Because these associations also appear to be independent of concomitant variability in “established” risk factors for CHD and atherosclerosis, such as hyperlipoproteinemia, elevated blood pressure, and (among human beings) cigarette smoking and age, the mechanism(s) mediating behavioral influences on coronary disease remain unclear.

In this regard, several investigators have proposed that recurrent activation of the sympathetic nervous system (such as occurs with intense behavioral arousal) may initiate or exacerbate atherogenesis, possibly via hemodynamic disturbances associated with abrupt rises in heart rate and blood pressure.10-13 Specifically, it has been hypothesized that cardiovascular responses to behavioral stimuli, if appreciable in magnitude and frequent in occurrence, may cause injury to the arterial endothelium.14,15 Such injury may then be followed by accumulation of plasma lipoproteins in the intima, the release of mitogenic substances by the damaged endothelium or by activated platelets, and intimal smooth muscle cell proliferation.16,17

If behavioral stimuli can potentiate atherogenesis through accompanying activation of the sympathetic nervous system, it is also reasonable to hypothesize that individuals exhibiting the most pronounced cardiovascular reactions under “stress” will similarly be at
heightened risk for exacerbated atherosclerosis. Such speculation is consistent, for example, with the observation that type A (“coronary prone”) individuals experience larger cardiovascular responses than do their type B (noncoronary-prone) counterparts when exposed to frustrating mental tasks or other psychological stressors.\textsuperscript{18, 19}

To the extent that cardiovascular responses to behavioral challenges may promote atherogenesis, it seemed reasonable to us that long-term administration of a \(\beta\)-adrenoreceptor--blocking agent would be protective against coronary artery atherosclerosis in the behaviorally predisposed individual. The purpose of the present experiment was to test this hypothesis in a study of male cynomolgus macaques fed a moderately atherogenic diet. All monkeys were housed for 2 years in repeatedly reorganized (i.e., stressful) social groupings; half of the animals were administered propranolol throughout the investigation, and the social status of each monkey was assessed on a recurrent basis. As noted above, socially dominant monkeys develop greater coronary atherosclerosis than do subordinates when both are housed under unstable social conditions.

To the extent that such effects might be mediated by cardiac responses to the stress of recurrent social reorganization, it may be predicted that untreated dominants in this study would have: (1) more extensive coronary artery atherosclerosis than similarly dominant monkeys receiving propranolol, and (2) as in previous experiments,\textsuperscript{8} more extensive atherosclerosis than subordinate animals, irrespective of the antiatherogenic effects of propranolol. The results reported here are consistent with the predicted effects.

**Methods**

**Animals.** The study animals were 30 male cynomolgus monkeys (Macaca fascicularis) imported from Singapore as adults (average age = 7.0 years, estimated by dentition). This species has a well-known susceptibility to diet-induced coronary artery atherosclerosis,\textsuperscript{20} and has previously proven useful in studies of behavioral influences on coronary artery atherosclerosis.\textsuperscript{8, 9, 21}

**Experimental design and procedures.** The 30 monkeys were assigned in equal numbers to either a propranolol-“treated” or “untreated” condition. Within each condition, monkeys were divided randomly into three five-member social groups, and all groups were housed in identical pens measuring 3.0 \(\times\) 3.2 \(\times\) 2.5 m (with outdoor exposure). Further, animals in both treatment conditions were fed a moderately atherogenic diet. This diet (table 1) derived 43\% of calories from fat and had a cholesterol concentration of 0.26 mg/calorie. Consumption of this diet resulted in a mean total serum cholesterol (TSC) concentration of 392 \(\pm\) 14 (SE) mg/dl across the study period. Animals were fed twice daily (at 8 A.M. and 2 P.M.) and received an amount sufficient to provide 150 calorie/kg of body weight/day. The duration of the experiment was 26 months, at the end of which animals assigned to both the treated and untreated conditions underwent autopsy. Of the 30 experimental animals, data from 24 contributed to analyses reported here. The remainder of animals were lost to the experiment, but equal numbers from the treated and untreated groups did not contribute data: four animals died prematurely of chronic infections unrelated to the study, one was removed from social housing for a lengthy period due to injury, and the arteries of a sixth monkey were damaged during preparation.

**Pharmacologic manipulation.** In the propranolol-treated group, propranolol was added to the animals’ diet in the amount of 0.2 mg/calorie/day (equivalent to a human dose of about 400 mg/day). Propranolol was included in the diet on a caloric basis because of the relatively high metabolic rates of cynomolgus monkeys (e.g., a 5 kg male consumes nearly one-third the calories of a 75 kg human being). The drug was administered throughout the 26 months of the experiment. Animals in the untreated group received only the atherogenic diet, were fed at the same time of day, and in all other respects were handled identically to propranolol-treated monkeys.

**Social housing.** We have previously observed that coronary artery atherogenesis in male cynomolgus monkeys is exacerbated when animals are exposed to a disrupted social environment.\textsuperscript{5, 9} In these studies, social disruption or instability was achieved by periodic redistribution of monkeys among social groups. The same social manipulation was used in the present experiment, with the reorganization of group memberships occurring on a monthly basis and following a schedule that permitted each monkey to be housed with either three or four new animals on every reorganization. Because the introduction of “strangers” is experienced as a threat to existing relationships among group members, animals exposed to periodic group reorganizations must frequently engage in behaviors aimed at reestablishing hierarchical associations and affiliative coalitions. To further heighten intragroup competition, an estrogen-implanted (sexually receptive), ovarioctomized female was also placed into each social group for the last 2 weeks of each 4 week reorganization.

**Psychosocial observations.** The behavioral repertoire of macaques living in small groups has been described previously by ourselves and others.\textsuperscript{8, 22-26} Briefly, this repertoire consists

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**TABLE 1**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>g/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein, USP</td>
<td>8.00</td>
</tr>
<tr>
<td>Lactalbumin</td>
<td>8.00</td>
</tr>
<tr>
<td>Wheat flour</td>
<td>35.44</td>
</tr>
<tr>
<td>Dextrin</td>
<td>6.00</td>
</tr>
<tr>
<td>Sucrose</td>
<td>5.00</td>
</tr>
<tr>
<td>Applesauce</td>
<td>4.50</td>
</tr>
<tr>
<td>Lard</td>
<td>9.50</td>
</tr>
<tr>
<td>Butter</td>
<td>3.00</td>
</tr>
<tr>
<td>Beef tallow</td>
<td>7.00</td>
</tr>
<tr>
<td>Dry egg yolk</td>
<td>3.50</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>0.50</td>
</tr>
<tr>
<td>Complete vitamin mixture</td>
<td>2.56</td>
</tr>
<tr>
<td>Ausman-Hayes mineral mixture</td>
<td>5.00</td>
</tr>
<tr>
<td>NaCl</td>
<td>2.00</td>
</tr>
</tbody>
</table>

\textsuperscript{8} Forty percent of calories derived from fat, 0.25 mg cholesterol/calorie. For the first 6 months of the study, animals consumed a diet that contained slightly less lard and egg yolk (equivalent to 0.19 mg cholesterol/calorie); the amount of cholesterol was increased to maintain the animals TSC concentrations between 350 and 400 mg/dl.
of a relatively limited number of stereotyped motor patterns that may be characterized as aggressive, submissive, or affiliative.\textsuperscript{8} Technicians recorded the occurrence of these motor patterns using a focal sampling technique\textsuperscript{22} in conjunction with an electronic data collection device (Electro General Corporation, Minnetonka, MN). A total of 206 focal samples (each 15 min in length) was taken on each experimental animal. Observations were made between 9 A.M. and 4 P.M., with times of day balanced across animals assigned to the treated and untreated groups. After their collection, data were transmitted to a VAX computer (DEC Corporation) for calculation of rates of performance (per hour, per monkey) for all discrete behaviors. In the statistical treatment of these data, appropriate transformations were applied when necessary to achieve normality of distribution and homogeneity of variances among the groups subject to comparison.

Determination of social status. As noted earlier, we have observed that animals of the highest social status develop the most extensive coronary artery atherosclerosis under the present conditions of housing.\textsuperscript{8} Social status or dominance refers to the relative abilities of individuals within social groups to defeat other group members in antagonistic encounters.\textsuperscript{30} Social status was determined, as in previous experiments, on the basis of fight outcomes among individuals.\textsuperscript{27} The aggression and submission matrices constructed for each of the experimental periods were used to determine the direction of fight outcomes for all pairings of animals in each social group. Winners of fights were judged dominant to losers. The one animal in each group that defeated all others, as evidenced by elicitation of flight gestures, was designated the first-ranking monkey. The monkey that defeated all but the first-ranking animals was labeled second ranking, and so forth.

For each social reorganization, the number of animals over which a given monkey was dominant was recorded as a dominance “score” for that animal. These scores were next averaged for each monkey over all experimental periods, and animals in each condition were ranked in the order of their scores. All animals falling above the median of the resulting distribution of social rankings were identified as dominant monkeys in the experiment; the remaining, lesser-ranked animals were designated subordinates. In instances involving ties (n = 1), a ratio of aggressive-to-submissive interaction served as a second discriminator. Importantly, differences in the social status of these monkeys were relatively stable over the course of the experiment, and equally so in both the treated and untreated groups. On the average, animals categorized as dominant were found to be high ranking in 81% of experimental periods among the propranolol-treated monkeys, and in 82% of experimental periods among untreated animals. Conversely, subordinate monkeys were found to be low ranking in 81% and 79% of experimental periods, respectively, in the treated and untreated groups.

Clinical observations

Serum lipid concentrations. Blood samples for determination of TSC and high-density lipoprotein cholesterol (HDL C) concentrations were taken 25 times during the study (approximately once per month). The TSC determinations (in mg/dl) were conducted by use of the AutoAnalyzer II procedure,\textsuperscript{28} while serum HDL C concentrations (in mg/dl) were assessed similarly after heparin manganese precipitation.\textsuperscript{29} All serum lipids were evaluated in our Lipid Analytic Laboratory, which is in complete compliance with the Cooperative Lipid Standardization program of the U.S. Department of Health and Human Services. Animals were fasted for 18 hr before sampling, and during sampling they were restrained with ketamine HCI (at a dose of 15 mg/kg).

Heart rate. Periodic heart rate and blood pressure measurements were obtained to determine the effectiveness of the pharmacologic treatment. Heart rate recordings were made in two separate contexts, referred to here as “controlled observations” and “casual measurements.” For all recordings, animals were first anesthetized and fitted with portable electrocardiographic (ECG) telemetry units (Keuffel & Esser, Model TM-8 patient monitors); these devices were secured beneath nylon mesh monkey jackets and maintained in place for several days. Heart rates were monitored in a laboratory space removed from the animals, and all measurements were taken on days following animals’ recovery from anesthesia.

For the controlled observations, animals’ heart rates were recorded under three standardized conditions, termed “baseline,” “stress,” and “minimal stimulation.”\textsuperscript{13} The baseline heart rates were obtained during a period of relative quiet when no human beings were visible to the monkeys. Stress heart rate measurements were collected during presentation by the experimenter of a standard 15 min challenge involving threatened capture. Heart rate measurements under minimal stimulation were obtained in the same setting (i.e., in the experimenter’s presence) but without threat. Heart rate recordings under these conditions were obtained on four occasions, once before assignment of animals to the treated and untreated groups (while animals were housed in five-member preexperimental groups) and at 9 month intervals thereafter.

The second context for heart rate evaluation, casual measurement, involved the continuous monitoring of heart rate over 15 consecutive hr (specifically, 6 P.M. to 9 A.M.). For purposes of analysis, heart rates recorded during these hours were collapsed to yield a single value for each monkey over the hours 6 P.M. to 11 P.M. (evening), 11 P.M. to 4 A.M. (night), and 4 A.M. to 9 A.M. (morning). Casual measurements were obtained on four occasions during the experiment, once before the drug treatment and during experimental periods 6, 15, and 24.

Animals’ preexperimental heart rates are summarized in table 2. As indicated in the table, monkeys subsequently assigned to the treated and untreated groups did not differ before the experiment on any of the heart rate measurements obtained (as revealed by unpaired t tests). This was true both of comparisons involving all 30 animals entered initially into the study and of the 24 monkeys whose data contribute to the primary analyses described in this report.

Blood pressure. The mean blood pressure (mm Hg) was recorded, while monkeys were sedated with ketamine, with the use of a Doppler ultrasound apparatus (Arteriosonde 1010, Roche). These measurements were taken on five occasions, once before animals’ assignment to conditions, and at 6 month intervals thereafter. Previous work in our laboratory has shown that indirect measurements of blood pressure recorded under ketamine anesthesia correlate well with blood pressure measurements obtained from the same animals under fully conscious conditions.\textsuperscript{30} Also shown in table 2 are the preexperimental blood pressures of animals later assigned to the treated and untreated groups; similar to the heart rate measures, there were no significant between-group differences in mean blood pressure before the experimental phase of the study.

Measurement of coronary artery atherosclerosis. At the time of autopsy, the heart of each monkey was removed and the coronary arteries were perfused with 10% neutral buffered formalin under a pressure of 100 mm Hg. After pressure fixation, 15 tissue blocks (each 3 mm in length) were cut perpendicularly to the long axis of the coronary arteries. Five serial blocks each were taken from the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). A section from each block was stained with Verhoeff van Giesen stain and projected, and the area occupied by intimal lesion (i.e., the area between the internal elastic lamina and the lumen of the artery) was measured by use of a computer-aided image analyzer (MOP

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TABLE 2
Preexperimental mean heart rates and blood pressures (±SE) of animals assigned to the treated and untreated groups

<table>
<thead>
<tr>
<th></th>
<th>Original sample (n = 30)</th>
<th>Final Sample (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Untreated</td>
</tr>
<tr>
<td>Heart rate on controlled observations (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>132 (7)</td>
<td>126 (5)</td>
</tr>
<tr>
<td>Stress</td>
<td>230 (5)</td>
<td>221 (6)</td>
</tr>
<tr>
<td>Minimal stimulation</td>
<td>160 (6)</td>
<td>162 (6)</td>
</tr>
<tr>
<td>Heart rate on casual measurements (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>124 (4)</td>
<td>123 (4)</td>
</tr>
<tr>
<td>Evening</td>
<td>112 (5)</td>
<td>110 (4)</td>
</tr>
<tr>
<td>Night</td>
<td>106 (4)</td>
<td>104 (4)</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>74 (2)</td>
<td>74 (3)</td>
</tr>
</tbody>
</table>

III, Zeiss Corporation). Previous work has demonstrated a high interobserver reliability (r = .96) for intimal area measurements obtained by this technique in our laboratory. Intimal area, as determined with an image analyzer, is the most commonly reported measure of extent of atherosclerosis in studies of non-human primates due to the precise and unbiased nature of its measurement. The extent of atherosclerosis in each section of each artery was highly correlated with the mean extent of lesion for that artery (LAD, r = .92; LCX, r = .96; RCA, r = .95). Hence, for purposes of analysis, the extent of coronary artery atherosclerosis for each animal was expressed as the mean intimal area (in mm²) calculated for each of the three coronary arteries. The extent of atherosclerosis in each individual artery was, in turn, highly correlated with the mean extent of lesion for each animal as determined for all 15 sections (LAD, r = .87; LCX, r = .93; RCA, r = .81).

Results

Coronary artery atherosclerosis. There were 12 dominant and 12 subordinate monkeys among the 24 animals whose data contribute to these analyses; further, the dominant and subordinate animals were distributed equally in the treated and untreated groups. The mean intimal areas (across all three coronary arteries) of dominant and subordinate animals in the treated and untreated groups are presented in figure 1, left. To determine whether dominance status or propranolol treatment influenced extent of coronary artery atherosclerosis, intimal area measurements were subjected to a 2-by-2-by-3 (experimental condition treated, untreated-by-status dominant, subordinate-by-artery LAD, LCX, RCA) analysis of variance; the three individual arteries (LAD, LCX, RCA) served as the repeated measure. Due to a somewhat skewed distribution of intimal area measurements, these data were first subjected to a linear transformation of the form X' = √X + 0.5. The subsequent analysis of variance showed no significant main effect for either experimental condition or status, but did yield a significant experimental condition-by-status interaction term (F[1,20] = 5.48, p = .028). A priori contrasts among group means (by Duncan’s multiple comparison procedure, at p < .05) revealed, as predicted, that dominant monkeys in the untreated group had significantly more coronary artery atherosclerosis at autopsy (untransformed mean = 0.71 mm²) than did animals comprising the three remaining groups (i.e., treated dominants [mean 0.23 mm²], and both treated and untreated subordinates [means 0.43 and 0.30 mm²]; figure 1); no significant differences were observed in pairwise comparisons among the latter three groups.

Hence, while socially dominant animals in the untreated group developed greater coronary artery atherosclerosis than their subordinate counterparts, the influence of social dominance on coronary atherogenesis was not evident among monkeys that had been administered propranolol over the course of the experiment. For purposes of comparison, figure 1 also depicts the mean atherosclerosis of dominant and subordinate monkeys from a prior experiment in which animals were autonomically intact (as in the untreated condition here), as well as housed in groups of rotating memberships and fed a cholesterol-containing diet. Notably, mean intimal area measurements of dominant and subordinate animals in the current untreated group closely replicate the corresponding values obtained in our previous experiment.

Finally, there was also a significant main effect for artery (F[2,40] = 4.89, p < .05), which reflected a greater extent of atherosclerosis in the LAD and LCX (means 0.44 and 0.51 mm²) than in the RCA (mean 0.31 mm²). However, the interactive effect of experimental condition and status on coronary artery atherosclerosis extended across all arteries, as evidenced by the absence of a significant condition-by-status-by-artery interaction (F[2,40] = 1.33, NS).

While extent of coronary artery atherosclerosis varied among groups, pathologic characteristics of the
lesions occurring in the four groups were qualitatively similar. In general, the intimal lesions contained extracellular lipid, numerous foam cells, and increased amounts of collagen and elastin. Accumulations of lipid, and occasionally mineralization, were noted as medial changes in the coronary arteries of some of the animals. The medial changes observed were comparable to those seen in other macaques fed equivalent diets.

**Clinical observations.** Serum lipid determinations and heart rate and blood pressure measurements obtained during the experiment were subjected to separate repeated-measures analysis of variance. These analyses involved two grouping factors — experimental condition (treated, untreated) and status (dominant, subordinate) — and a variable number of repeated measures, depending on the frequency with which each variable was sampled over the course of the study (as described above). In none of these analyses did the repeated measure vary as a function of experimental condition, social status, or the interaction of these two factors. Therefore, the tabular summary of data (tables 3 and 4) presents mean values (±SE) collapsed across all measurements obtained during the course of the experiment. To the right of the tabled means are listed summary statistics for the main effects of experimental condition and status, and the experimental condition-by-status interaction term.

**Serum lipid concentrations.** As shown in table 3, TSC concentrations were in the range of 380 to 400 mg/dl for all experimental groups, while HDLC concentrations varied only between about 35 and 40 mg/dl. On neither variable did the analysis of variance yield a significant main effect of experimental condition or status, or a significant interaction of condition and status. Not surprisingly, mean TSC and HDLC concentrations correlated appreciatively with extent of coronary artery atherosclerosis; this was true across all experimental animals (TSC, \( r = .63 \), \( p < .01 \), two-tailed probability; HDLC, \( r = -.51 \), \( p < .01 \)), as well as in the treated and untreated groups separately (TSC, \( r = .69 \), \( p < .02 \), untreated; \( r = .72 \), \( p < .01 \), treated; HDLC, \( r = -.55 \), \( p > .05 \), untreated; \( r = -.50 \), \( p < .10 \), treated). Due to these associations, the effects of experimental condition and of social status on coronary artery atherosclerosis were reexamined by analysis of covariance, entering both TSC and HDLC as covariates. As in the previously reported analysis of variance, the analysis of covariance revealed no reliable main effect of either experimental condition or status. Moreover, the experimental condition-by-status interaction term was again significant (F[1,18] = 12.64, \( p < .01 \)), indicating that the interactive influences of propranolol administration and social dominance on coronary artery atherogenesis could not be accounted for by concomitant variability in serum lipid concentrations among these experimental animals.

**Heart rate and blood pressure.** There were no preexperimental differences between the treatment groups in either heart rate or mean blood pressure. However, it

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**TABLE 3**

<table>
<thead>
<tr>
<th></th>
<th>Treated dominant (n = 6)</th>
<th>Treated subordinate (n = 6)</th>
<th>Untreated dominant (n = 6)</th>
<th>Untreated subordinate (n = 6)</th>
<th>Main effects</th>
<th>Interaction: experimental condition-by-status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSC (mg/dl)</strong></td>
<td>383 (45)</td>
<td>383 (80)</td>
<td>399 (33)</td>
<td>400 (17)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HDLC (mg/dl)</strong></td>
<td>36 (5)</td>
<td>40 (11)</td>
<td>35 (9)</td>
<td>35 (5)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Logarithmic transformation used.
was expected that during the experiment, propranolol-treated animals would have significantly lower heart rate and blood pressure than untreated controls. As indicated in table 4, this prediction was supported across all heart rate and blood pressure recordings; in each instance the analysis of variance revealed a highly significant main effect of experimental condition. For heart rate, mean values on baseline (as seen in the "controlled observations") were 20 to 25 beats/min lower among the monkeys administered propranolol relative to their untreated counterparts. Interestingly, this difference was even more appreciable in measurements obtained during provocation of the animals (i.e., under stress), when sympathetic nervous influences on myocardial performance would be most pronounced. The "casual" heart rate measurements revealed a similar pattern of significant differences between treated and untreated animals. Finally, heart rate as measured under these conditions did not vary as a function of status, or of the interaction of experimental condition and status.

Like heart rate, mean blood pressure measurements (although recorded under ketamine anesthesia) were significantly lower in the propranolol-treated condition than among untreated controls (table 4). This difference averaged 14 mm Hg across all blood pressure measurements. In contrast, blood pressure did not differ reliably between dominant and subordinate animals, nor was there a significant experimental condition-by-status interaction.

**Psychosocial observations.** It was expected that socially dominant animals would engage in aggression more frequently than subordinates, and that the ratio of aggressive to submissive acts would vary similarly as a function of animals' social status. We did not expect affiliative behavior to differ overall between dominant and subordinate monkeys, nor did we predict any specific effects of the administration of propranolol on animals' social behaviors. Results of analyses of variance based on these behavioral indexes, as collected over the course of the experiment, are presented in table 5. Note that all antagonistic behaviors — mild and contact aggression, the aggression-to-submission ratio — successfully discriminated between dominant and subordinate animals. That these effects were not qualified by the experimental condition to which animals had been assigned is indicated by the absence of any significant experimental condition-by-status interactions. Moreover, administration of propranolol itself was associated with no reliable differences in the antagonistic or affiliative behaviors of these animals.

**Discussion**

Cynomolgus macaques fed atherogenic diets have been shown previously to be a suitable preparation of occlusive atherosclerotic disease of the coronary

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**TABLE 4**

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Mean heart rates (bpm) and blood pressure (mm Hg) (±SE) of dominant and subordinate animals in the treated and untreated groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated dominant (n = 6)</td>
</tr>
<tr>
<td>Heart rate on controlled observations</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>101 (6)</td>
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<tr>
<td>Stress</td>
<td>158 (10)</td>
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<tr>
<td>Minimal stimulation</td>
<td>113 (8)</td>
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<tr>
<td>Heart rate on casual measurements</td>
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<td>Morning</td>
<td>104 (6)</td>
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<td>Evening</td>
<td>92 (5)</td>
</tr>
<tr>
<td>Night</td>
<td>87 (5)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>68 (9)</td>
</tr>
</tbody>
</table>
arteries. This species is also useful for experimental evaluations of psychosocial influences on atherogenesis because two prominent dimensions of the macaque’s behavioral repertoire — competitiveness and aggression — are analogous to aspects of social behavior thought to contribute to CHD in human beings. Earlier findings from our laboratory demonstrate that, when fed a cholesterol-containing diet and housed in periodically reorganized social groupings, highly aggressive and competitive (dominant) male cynomolgus monkeys develop exacerbated coronary artery atherosclerosis. The current experiment replicates this association in the animals assigned to the untreated group. Additionally, the present data demonstrate that long-term administration of propranolol retards the development of coronary artery atherosclerosis, and does so specifically among dominant animals.

Other studies have shown that propranolol has antiatherogenic effects in the aortas of cholesterol-fed normotensive and hypertensive rabbits. However, in one study, propranolol had no significant effect on the coronary artery atherosclerosis of stump-tailed monkeys (Macaca arctoides). It is possible that the absence of an antiatherogenic effect in this latter experiment was due to the relatively small dose of propranolol administered to animals (less than one-half the dose used in the current study). Also, the present data suggest that propranolol may only have a retarding effect on atherogenesis in some animals (e.g., dominants), and then only among animals exposed to those social environments that potentiate behavioral influences on atherogenesis (e.g., within disrupted social groupings).

Notably, the psychosocial and pharmacologic effects on coronary atherogenesis in the current experiment were independent of concomitant variations in serum lipids. Similarly, behavioral influences on atherogenesis were found to be unrelated to variability in serum lipid concentrations in two of our previous studies. The effect of psychosocial factors on CHD in human beings (particularly as related to type A behavior and hostility) is also independent of variability in serum lipids. In this regard, the absence of a deleterious effect of propranolol on HDLC concentrations should be mentioned, since such an effect occasionally has been observed in human beings. The HDLC concentrations of macaques exposed to a cholesterol-containing diet are already low (e.g., < 40 mg/dl), and may well be resistant to further pharmacologic reduction.

In the absence of a lipid-mediated treatment effect, other mechanisms must account for the selective influence of propranolol on atherogenesis in dominant animals. β-Adrenergic–blocking agents differ in lipophilicity and thus in their propensity to cross the blood-brain barrier. As a lipophilic β-blocker, propranolol might have exerted a significant influence on those behaviors associated with risk for coronary artery atherosclerosis (e.g., aggression) due to such central nervous system penetration. However, frequent monitoring of the stereotyped motor patterns typically performed by these monkeys revealed no effects of the drug on animals’ antagonistic or affiliative behavior, either overall or in relation to differences in social status. Hence, the current data do not provide support for the speculation that propranolol selectively affected the behavior, and thereby the atherosclerosis, of dominant animals.

Likewise, the generalized effects of propranolol on blood pressure and heart rate, which occurred irre-
spective of social status, cannot account for the selective protection accorded dominant animals in the treated groups. These particular heart rate and blood pressure assessments were obtained under the customary and controlled conditions of laboratory measurement (i.e., under anesthesia or at times of convenience to the investigator). However, the atherogenicity of psychosocial factors may result from the marked hemodynamic and/or metabolic adjustments experienced by susceptible animals during naturally occurring periods of social challenge or stress (e.g., competitive encounters). Such physiologic responses are likely to be acute and transient in nature, and therefore elude detection in measurements recorded under usual laboratory conditions. Of particular relevance is our observation in this species that naturally occurring social encounters among group members elicit significant changes in heart rate, and that during active periods of social reorganization such changes are significantly more pronounced in dominant than subordinate monkeys. We hypothesize that propranolol may have exerted an antiatherogenic influence in this study by moderating hemodynamic or metabolic manifestations of a sympathetic nervous system response experienced most appreciably by dominant animals during recurring, although spontaneous, social challenges.

While there may exist other explanations for the present findings, any such explanation must account for propranolol’s delimited influence on the coronary artery atherosclerosis of dominant animals. In turn, the fact that both the exacerbation and propranolol-induced inhibition of atherosclerosis were observed only in animals that often show the largest cardiac responses to stress (i.e., dominants) suggests (as noted above) that arousal of the sympathetic nervous system is responsible, to some extent, for modulating the influence of behavioral factors on coronary atherosclerosis in this animal preparation. We thus conclude that treatment with β-adrenergic blockers may confer a degree of protection against coronary artery atherosclerosis among individuals behaviorally predisposed to CHD.

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