Prednisone Increases Low Density Lipoprotein in Cynomolgus Monkeys Fed Saturated Fat and Cholesterol

Walter H. Ettinger, Robert C. Dysko, and Thomas B. Clarkson

Cynomolgus monkeys were given prednisone to determine its effects on lipoprotein metabolism and other risk factors for atherosclerotic cardiovascular disease. After 1 month of oral prednisone, the mean total plasma cholesterol (TPC) concentration increased from 240±36 to 476±78 mg/dl (p<0.01) in animals fed a diet containing 36% of calories as fat (polyunsaturated/monounsaturated/saturated, 1.0:3.9:4.1) and cholesterol (0.39 mg/kcal). The increase in TPC was due to higher concentrations of the apolipoprotein B (apo B)-containing lipoproteins, particularly low density lipoprotein (LDL). LDL cholesterol concentrations also increased in animals fed a diet containing saturated fat and 0.25 mg/kcal of cholesterol, as well as in animals fed monkey chow. Kinetic studies of LDL indicated both an increased flux of apo B into LDL and a decrease in the fractional catabolic rate of LDL. Mean high density lipoprotein cholesterol (HDL-C) concentration decreased from 48±8.2 to 14±4 mg/dl, p<0.001, in animals fed fat and cholesterol, but there was no significant change in HDL-C in animals fed monkey chow. Blood pressure, fasting serum glucose, and anthropometric measures did not change after 7 months of prednisone therapy. Prednisone increases LDL concentration in the cynomolgus monkey. This animal may be a good model for studying corticosteroid dyslipoproteinemia, and possibly atherosclerosis, in an immunosuppressed host.


Atherosclerotic vascular disease is an important clinical problem in a diverse group of patients who are treated with immunosuppressive agents. However, the pathogenesis of atherosclerosis in such patients is not well understood, and there is little information about the risk factors for atherosclerotic coronary artery disease (CAD) in these patients. A major question that remains to be answered is whether corticosteroids as immunosuppressive agents contribute to the development and progression of CAD. Corticosteroids are known to exacerbate some CAD risk factors such as hypertension, glucose intolerance, and hyperlipidemia. However, it has been argued that administration of corticosteroids may result in lipoprotein changes such as hypertriglyceridemia, which is not an important CAD risk factor, or may increase plasma levels of high density lipoprotein (HDL), which lessens the risk of CAD. Furthermore, it has been suggested that corticosteroids may protect against atherosclerosis by preventing the uptake of lipids in the arterial wall.

One of the major obstacles to resolving the controversy regarding corticosteroids and atherosclerosis is the difficulty of studying risk factors and development of CAD in immunosuppressed patients with complex illnesses. Nearly all studies that address the relationship between corticosteroids and risk of CAD are complicated by variability in the dose and duration of corticosteroid treatment, by varying age and sex of patient groups, by high prevalence of confounding medical conditions (such as acute illness, diabetes, renal insufficiency, hypertension), and by other medications that affect lipid metabolism. Studies of corticosteroids in normal volunteers are of limited value, because the numerous side effects of these drugs limit the duration of drug treatment.

For these reasons, an animal model may be useful for study of the effects of corticosteroids on atherosclerosis and its risk factors. In this report, we present data on the effects of corticosteroids on CAD risk factors and emphasize plasma lipoproteins in the female cynomolgus monkey, Macaca fascicularis, fed a diet high in saturated fat and supplemented with cholesterol. This species was chosen because it is a good model for diet-induced hyperlipidemia and atherosclerotic CAD and because other animal models, such as rabbits and rats, do not respond to corticosteroids in a manner similar to human beings.

Methods

Study Design

The animals used in the study were colony-born, female cynomolgus monkeys, 2 to 3.5 years old, 1.9 to 3.2 kg in weight, that lived in harem colony units.
Table 1. Composition of Diets Fed to Cynomolgus Monkeys

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Grams/100 g</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Carbohydrate (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purina monkey chow-25</td>
<td>75.70</td>
<td>19.3</td>
<td>3.86</td>
<td>39.06</td>
</tr>
<tr>
<td>Dry egg yolk</td>
<td>8.20</td>
<td>1.8</td>
<td>5.41</td>
<td>0.21</td>
</tr>
<tr>
<td>Brewer’s yeast</td>
<td>4.00</td>
<td>1.48</td>
<td>0.06</td>
<td>1.50</td>
</tr>
<tr>
<td>Raw wheat germ</td>
<td>2.00</td>
<td>0.50</td>
<td>0.20</td>
<td>0.99</td>
</tr>
<tr>
<td>Lard</td>
<td>10.00</td>
<td></td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td><strong>Diet B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casein, USP</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactalbumin</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat flour</td>
<td>35.5</td>
<td>3.72</td>
<td>0.36</td>
<td>30.2</td>
</tr>
<tr>
<td>Dextrin</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>5.0</td>
<td></td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Applesauce</td>
<td>4.5</td>
<td>0.02</td>
<td>Trace</td>
<td>1.08</td>
</tr>
<tr>
<td>Lard</td>
<td>9.5</td>
<td></td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td>3.0</td>
<td>0.01</td>
<td>2.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Beef tallow</td>
<td>7.0</td>
<td></td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Dry egg yolk</td>
<td>3.5</td>
<td>0.77</td>
<td>2.24</td>
<td>0.09</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>0.5</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td><strong>Diet C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purina monkey chow-25</td>
<td>100.0</td>
<td>19.3</td>
<td>3.86</td>
<td>39.06</td>
</tr>
</tbody>
</table>

**Diet A**

The first part of the study was a prospective trial of orally administered prednisone to determine the effects of chronically administered corticosteroids on CAD risk factors. Seven animals were used in this part of the study, which was 11 months long. These animals were selected to represent both hypo- and hyperresponders to dietary cholesterol. The animals consumed a diet which provided 36% of calories as fat [polyunsaturated/monounsaturated/saturated (P/M/S), 1.0:3.9:4.1], 34% of calories as carbohydrate, 19% calories as protein, and 0.39 mg/kcal of cholesterol (Diet A in Table 1). The animals were fed 150 kcal/kg/day in two feedings at 8:00 A.M. and 2:00 P.M. During the first 2 months, the animals were not given prednisone, and measurements were made of plasma lipoproteins, serum glucose, blood pressure, and anthropometric variables. During the next 6.5 months, the animals were given prednisone twice daily mixed in the diet. The initial dose of prednisone was 0.022 mg/kcal/day, which was given for 3 months. The amount was chosen to represent the equivalent of 40 mg of prednisone per day in a 50 kg human woman and was based on the relative caloric requirements of humans and monkeys. The daily prednisone dose was then reduced to 0.011 mg/kcal/day for 2 months, and finally to 0.0055 mg/kcal/day for 1.5 months. The third phase of the study was a drug-free period of 2.5 months. Plasma lipoprotein concentrations, blood pressure, and weight were measured monthly. Serum glucose was measured every 3 months, and skinfold thickness and a ponderosity index were measured once during each phase of the study.

**Diet B**

The second part of the study was a prospective trial of five animals who were fed a synthetic diet (150 kcal/kg/day divided into two feedings) to provide 43% of calories as fat (P/M/S, 1.0:3.3:2.8), 39% of calories as carbohydrate, 18% as protein, and 0.25 mg/kcal of cholesterol (Diet B in Table 1). Plasma lipids were measured and low density lipoprotein (LDL) apolipoprotein (apo) B turnover studies were carried out before and after the 6-week prednisone treatment (0.011 mg/kcal/day). For these studies, the animals were housed in individual cages. One week before the start of a metabolic study, the animals were habituated to wearing a monkey jacket with a 3-foot tether line that attached to the back of the cage (Alice King Chatam, Incorporated, Los Angeles, CA). At 4 days before the study, each animal was anesthetized, a sterile Tygon cannula (0.03 inches inside diameter) was inserted into a femoral artery and vein, and the cannula was threaded through the tether line and out the back of the cage. The lines were kept patent by a constant saline infusion. The animals were fasted overnight before the turnover studies and were then fed their usual diets beginning with the 2:00 P.M. feeding on Day 1. Radiolabeled LDL was injected through the venous catheter, and 2 ml blood samples were obtained from the arterial catheter for radioiodine counts at 3, 30, and 90 minutes and 3, 6, 9, 24, 48, 72, and 96 hours after injection.

**Diet C**

The third part of the study was a prospective trial of five animals who consumed a standard monkey chow diet, 150 kcal/kg/day in two divided feedings (Diet C in Table 1). These experiments were undertaken to determine if changes in lipoprotein concentration occurred in animals fed a diet low in fat and free of cholesterol. Plasma lipoproteins were measured before and at 6 weeks after treatment with prednisone (0.011 mg/kcal/day).
Laboratory Measurements

Measurements of weight and blood pressure and blood collection were made after animals were anesthetized intramuscularly with 15 mg of ketamine. Weights were obtained with a spring scale, and blood pressure was measured in a lower limb with a Dynamap blood pressure monitor. The anthropometric profile included a ponderosity index (weight (g)/trunk length (cm)) and measures of the subscapular and triceps skinfold.22 Fasting serum glucose was measured using a Beckman glucose analyzer.

Blood for lipoprotein measurements was collected after an overnight fast into tubes containing 0.1% ethylenediaminetetraacetic acid (EDTA), 0.02% NaN₃, and 0.05% 5',5'-dithiobis-(2-nitrobenzoic acid). The plasma was separated from the cells by using low-speed centrifugation and was refrigerated at 4°C until analyzed. Very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and LDL were isolated by sequential ultracentrifugation.23 HDL was isolated by precipitation of apo B containing lipoproteins with dextran sulfate-magnesium chloride.24 Cholesterol (C) and triglyceride (TG) were measured by enzymatic methods. Apo E was measured by an enzyme-linked immunosorbent assay (ELISA), and apo B and apo A-I, by radial immunodiffusion.13,25 Lipoprotein subfraction heterogeneity was measured by nondenaturing gradient gel electrophoresis.26,27 The d<1.225 fraction of 2 ml of plasma was applied to 2% to 16% polyacrylamide gels to measure LDL heterogeneity and to 4% to 30% gels to measure HDL heterogeneity. After electrophoresis, gels were stained with Coomassie blue G-250, then washed and scanned with a densitometer. The molecular weight of the LDL peaks was calculated from the migration of an LDL of known molecular weight, thyroglobulin, apoferritin, catalase, lactate dehydrogenase, and bovine serum albumin. The Stokes' radius of the various HDL subfractions was determined in a similar manner.

For kinetic studies, the animal's LDL was isolated by sequential ultracentrifugation at a density of 1.020 to 1.050. The LDL was radiolabeled with 125I by using iodine monochloride and was filtered through a 45 μm Millipore filter before injection.23,28 After injection, the LDL from the timed plasma samples were isolated with a VT-65 rotor. One milliliter of plasma was adjusted to a density of 1.225 with KBR and then was overlayed with an NaCl solution of d=1.006. The samples were subjected to centrifugation for 65 minutes at 50 000 rpm, and the gradient fractions were isolated by puncturing the bottom of the tube and pumping Florinert into the tubes. The LDL peak was identified from the absorbance profile at 280 nm and the radioactivity in the fractions; the fractions then were pooled for further analyses. Radioactivity in LDL apo B was isolated by isopropanol precipitation.29

Statistical Analyses

Statistical comparison of multiple means was done with an analysis of variance or analysis of variance with repeated measures, and a comparison of two means was done by Student's t test. A p value ≤0.05 was considered to be statistically significant. Analyses of kinetic studies was done by a two-compartment model of LDL apo B and the SAAM 29 modeling program on a DEC VAX 11/750 computer.30

Results

There were no significant changes in blood pressure, anthropometric measures, or fasting glucose concentrations before, during, or after treatment with prednisone in the animals who consumed Diet A (Table 2). In contrast, there were pronounced changes in plasma lipoprotein concentrations during prednisone treatment (Figure 1). The mean total plasma cholesterol concentration increased from 240±36 to 476±78 mg/dl after 1 month of prednisone treatment and remained elevated throughout the treatment period. The cholesterol concentration did not change significantly when the dosage of medication was decreased but returned to near pretreatment levels.

Table 2. Blood Pressure, Fasting Serum Glucose, and Anthropometric Variables in Seven Monkeys Fed Diet A

<table>
<thead>
<tr>
<th>Variables</th>
<th>Month 1</th>
<th>Month 8</th>
<th>Month 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic/diastolic blood pressure (mm Hg)</td>
<td>(115±9)/(59±5)</td>
<td>(109±7)/(67±7)</td>
<td>(112±4)/(52±4)</td>
</tr>
<tr>
<td>Ponderosity index (g/cm)</td>
<td>95.4±6.2</td>
<td>101.1±9.4</td>
<td>97.7±3.4</td>
</tr>
<tr>
<td>Subscapular/triceps skinfold ratio</td>
<td>2.2±0.8</td>
<td>2.0±0.6</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>Fasting serum glucose (mg/dl)</td>
<td>81±5</td>
<td>75±6</td>
<td>70±3</td>
</tr>
</tbody>
</table>

Values are means±SE.
(311 ±46 mg/dl) within 6 weeks after prednisone was discontinued.

The increase in total plasma cholesterol concentration was due to an increase in the concentrations of the apo B-100-containing lipoproteins (Figure 2). After 6 months of treatment, the mean concentration of LDL-C had increased from 159±31 to 341±38 mg/dl, \( p<0.05 \), and that of VLDL-C from 10±6 to 38±16 mg/dl, \( p<0.05 \). In parallel, the concentrations of apo B (147±46 vs. 248±15 mg/dl, \( p<0.01 \)) and apo E (7.2±3 vs. 12.4±2 mg/dl, \( p<0.01 \)) increased significantly. Plasma triglyceride concentrations increased moderately during corticosteroid treatment, 26±7 vs. 46±11, \( p<0.07 \). The animals who consumed Diet B also had a marked increase in total plasma cholesterol (TPC) (203±30 mg/dl vs. 351±51, \( p<0.05 \)) and LDL-C (144±34 mg/dl vs. 291±49, \( p<0.01 \)) after treatment with prednisone. Similarly, the five animals fed monkey chow (Diet C) had an increase in TPC (203±30 mg/dl vs. 351±51, \( p<0.05 \)) and LDL-C (79±11 mg/dl vs. 130±12, \( p<0.01 \)) after prednisone treatment (Figure 3).

The molecular weight of LDL increased with prednisone treatment in monkeys fed Diet A. As shown in Figure 4, the migration distance of LDL on 2% to 16% polyacrylamide gels was less during treatment with prednisone, and the calculated mean molecular weight of the largest LDL peak increased from 3.2±0.2 to 4.2±0.1 g/μmol (\( p<0.01 \)).

To determine the mechanism of the increased LDL concentrations after corticosteroid treatment, tracer kinetic studies of radiolabeled LDL were undertaken in the five animals fed Diet B before and during prednisone administration. In four of five animals, there was a lower fractional catabolic rate (FCR) for LDL during prednisone administration (Figure 5). However, the flux of apo B into LDL also was significantly increased from 1.4±0.13 to 2.0±0.27 mg/kg/hr after prednisone treatment (Table 3).

In contrast to the apo B-containing lipoproteins, plasma HDL concentrations fell with prednisone administration in animals fed the diets containing saturated fat and cholesterol. After 1 month of prednisone, there was a 60% reduction in HDL-C (Figure 1) in animals fed Diet A.
Migration Distance from Origin

Figure 4. Densitometric scan of low density lipoprotein (LDL) nondenaturing gradient gel electrophoresis from Animal #4, fed Diet A, before (—) and after (—) 6 months of prednisone. This migration of the major peaks (arrows) was used to calculate the molecular weights of LDL from an LDL of known molecular weight and protein standards.

Discussion

One of the principle aims of this study was to determine the effect of chronically administered corticosteroids on risk factors for CHD in the cynomolgus monkey. The results show that corticosteroids have a marked effect on lipoprotein metabolism. Plasma cholesterol, LDL-C, and LDL molecular weight increased, while HDL levels decreased, during prednisone treatment in cynomolgus monkeys fed a diet containing saturated fat and cholesterol. Such changes in lipoproteins increase the risk of developing atherosclerosis in the nonhuman primate. In contrast, there was no demonstrable effect on other CAD risk factors: body weight, body fat distribution, fasting serum glucose, and blood pressure. While more sensitive measures may be needed to detect changes in these risk factors (such as a glucose tolerance test), these data suggest that the dyslipoproteinemia is potentially the more important risk factor for CAD caused by corticosteroids. It is likely that there would be progression in the extent of coronary artery atherosclerosis in these animals if these lipoprotein abnormalities persisted over a 24- to 36-month period.17,18 While anatomic studies are necessary to confirm this hypothesis, this study suggests that the cynomolgus monkey may be a model for examining the effects of corticosteroids on the development of atherosclerosis and its risk factors in an immunosuppressed host.

The increased concentrations of LDL-C, apo B, and apo E in these otherwise healthy animals are analogous to what has been reported in a diverse group of humans taking long-term corticosteroids.6,11-14,31,32 The slight increase in TG concentration is also consistent with what occurs in humans, because most human beings treated with corticosteroids have only moderate increases in TG concentration.6,9,11,12 Marked hypertriglyceridemia is usually seen in patients with underlying diabetes or renal insufficiency.6,33 Nonetheless, the absolute plasma levels of VLDL are considerably lower, and the composition of VLDL is different, in the cynomolgus monkey fed saturated fat and cholesterol than in humans. The plasma VLDL in these monkeys is relatively enriched in cholesterol ester and depleted of TG, and when plasma cholesterol levels exceed 500 mg/dl, a β-migrating VLDL is present.19 Therefore, caution is indicated when drawing a parallel between the two species.

The effect of the type and quantity of dietary fat and cholesterol on the dyslipoproteinemia caused by corticosteroids is an important question. This study suggests that while the quantity and quality of dietary fat and cholesterol may modify the magnitude of change in LDL levels,
Table 3. Low Density Lipoprotein Kinetic Data before and during Prednisone Treatment In Monkeys Fed Diet B

<table>
<thead>
<tr>
<th>Animal</th>
<th>Control</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPC (mg/dl)</td>
<td>Apo B (mg/kg)</td>
</tr>
<tr>
<td>1</td>
<td>286</td>
<td>46.5</td>
</tr>
<tr>
<td>2</td>
<td>135</td>
<td>23.6</td>
</tr>
<tr>
<td>3</td>
<td>282</td>
<td>42.3</td>
</tr>
<tr>
<td>4</td>
<td>167</td>
<td>26.7</td>
</tr>
<tr>
<td>5</td>
<td>144</td>
<td>30.5</td>
</tr>
<tr>
<td>Mean</td>
<td>203</td>
<td>34.3</td>
</tr>
<tr>
<td>±SD</td>
<td>±67</td>
<td>±6.6</td>
</tr>
</tbody>
</table>

*TPC = total plasma cholesterol, Apo B = apolipoprotein B, FCR = fractional catabolic rate, ACR = absolute catabolic rate.

prednisone increases LDL levels regardless of the type of diet fed to cynomolgus monkeys. The animals in these experiments were fed diets containing a wide range of cholesterol and fat, but in all 17 animals given prednisone, LDL levels increased within 6 weeks. This may be important clinically, because dietary modification is the first mode of treatment of hypercholesterolemia. There are data that suggest that dietary therapy is moderately effective in decreasing LDL-C in renal transplant patients treated with corticosteroids (Robert Moore, unpublished observations). However, in a study of heart transplant patients, who were prescribed a diet low in fat and cholesterol, development of hypercholesterolemia after transplantation was still a significant problem. 35 The interactions of dietary intake and corticosteroids on lipoprotein metabolism is an important topic for future study.

There is little information about the mechanism of corticosteroid dyslipoproteinemia in animals or human beings. To investigate the cause of the increased LDL concentrations in these monkeys, kinetic tracer studies of LDL apo B were undertaken. These data indicated that the increase in LDL concentrations during prednisone treatment may be multifactorial, since there was both a decrease in removal of LDL apo B and an increase in flux of apo B into LDL. Whether or not the decrease in FCR is a direct effect of corticosteroids on LDL receptor or nonreceptor uptake of LDL is unknown. In vitro experiments have suggested that corticosteroids impair both LDL binding to the LDL receptor and internalization of the LDL receptor-ligand complex. 36,37 If receptor-mediated removal of both VLDL and LDL were impaired by corticosteroids, this could account for the apparent increase in LDL production and removal, because a higher fraction of VLDL would be converted to LDL. However, there are data to indicate that hepatic secretion of VLDL is increased by corticosteroids. Thus, if secretion of VLDL is increased and the rate of conversion of VLDL to LDL is unchanged, the flux of apo B into LDL would be increased. The resultant increase in LDL concentration may then result in a down-regulation of the LDL receptor, further increasing LDL concentrations. 38 It is well known that LDL is a heterogeneous lipoprotein, and recent evidence suggests that the various LDL subfractions are catabolized at different rates. 40,41 Thus, it is possible that corticosteroids cause a change in the distribution of LDL subfractions in

Figure 6. Densitometric scan of high density lipoprotein nondenaturating gradient gel electrophoresis from Animal #7, fed Diet A, before (upper) and after (lower) 6 months of prednisone. Stokes' radii were calculated from protein standards of known size.
such a way that there is a greater percentage of LDL particles with a slower FCR. The changes in apo B metabolism do not completely explain the increase in plasma cholesterol, because the size of the LDL particle, and therefore the cholesterol ester content of the LDL particles, is also increased with corticosteroids. Thus, it seems likely that in prednisone-treated animals, there is more cholesterol ester being secreted by the liver or an increase in generation of cholesterol esters in plasma by lecithin-cholesterol acyltransferase.

Prednisone caused the HDL-C and apo A-I concentrations to decrease in the monkeys fed a saturated fat diet. However, the interpretation of this observation is complex, since HDL-C levels exhibit a biphasic response to fat and cholesterol feeding in monkeys; HDL-C rises until total cholesterol reaches concentrations of 200 to 300 mg/dl but then declines as total cholesterol levels become higher. Thus, the HDL-C concentrations in prednisone-treated animals may be depressed due to the marked hypercholesterolemia. In support of this hypothesis, chow-fed animals did not have a significant change in HDL-C concentrations. However, several animals who were fed the saturated fat and cholesterol diets and whose total cholesterol on prednisone was less than 300 mg/dl exhibited a fall in HDL-C, suggesting a direct effect of the drug. Several studies have shown HDL concentrations to be low in humans receiving corticosteroids, although there are reports of an increase in HDL after short-term corticosteroid treatment. However, it is difficult to interpret these data in human beings because of a number of confounding factors in the subjects who have been studied. These include: varying doses and times of administration of corticosteroids and the presence of renal disease, inflammatory processes, and varying states of nutrition in the patient groups. Taken altogether, these observations suggest that the HDL concentrations in immunosuppressed patients are influenced by several factors, including corticosteroids, underlying disease, other treatment modalities, body weight, and diet.

In conclusion, prednisone increases the LDL in the cynomolgus monkey, but the hyperlipidemic effects appear to be reversible and, in part, determined by diet.

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Index Terms: corticosteroids, lipoproteins, non-human primate.
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