Suppression of Adjuvant Arthritis in Rats by Cholesterol
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Abstract—Dietary cholesterol suppressed adjuvant arthritis, a chronic inflammatory disease, in rats, but did not significantly affect carrageenin edema, an acute inflammation. When rats were fed a high-cholesterol diet beginning 10 days before injection of adjuvant, the development of the adjuvant-induced arthritis was greatly suppressed. Cholesterol feeding prevented hypertrophy of the adrenal gland in arthritic rats, but had little influence on the serum corticosterone level. A significant positive correlation was observed between the adrenal weight and the severity of the arthritis. These findings suggest that the effect of cholesterol feeding is not due to increased adrenal steroid synthesis. Dietary cholesterol also prevented hypertrophy of the spleen, but had no effect on atrophy of the thymus in adjuvant-treated rats. Cholesterol-fed rats showed a significant decrease in the serum lipid peroxide level and a significant increase in the serum copper level. Adjuvant treatment not only enhanced hypercholesterolemia produced by cholesterol feeding, but also the level of free cholesterol in serum. These results suggest that dietary cholesterol may exert some effect on the immune response through changes in spleen and liver functions.

Adjuvant arthritis in rats is an inflammatory chronic disease which is induced by the injection of heat-killed mycobacteria (1, 2). It has been widely used as a model of human rheumatoid arthritis (3–5). The development of adjuvant arthritis is thought to be mediated by immunological mechanisms (6). In previous studies, while examining a convenient animal model of atherosclerosis, we discovered that adjuvant arthritis was suppressed in hypercholesterolemic rats (7). However, little is known about the anti-inflammatory effects of cholesterol. Serum cholesterol, a lipoprotein bound in circulating blood, can modify the composition and fluidity of the membranes of immunocompetent cells such as lymphocytes and macrophages. Recent evidence suggests that dietary cholesterol may in some way be involved in the immune responses (8–11). Cholesterol also serves as the precursor of all steroid hormones. Studies in humans (12) and rats (13) show that a considerable amount of the cholesterol substrate for adrenal steroidogenesis may come from plasma. Corticosteroids have an extremely important action in counteracting the inflammation. Thus, there are a variety of mechanisms by which cholesterol may interact with the induction process of adjuvant arthritis.

In the present study, we attempted to elucidate the mechanisms of the suppressive effects of dietary cholesterol on adjuvant arthritis in rats by assessing the changes in biochemical parameters and various organ weights relevant to the response of chronic inflammatory disease.

Materials and Methods
Animals and diet: Five-week-old male inbred Fischer F344/N rats (Shizuoka Laboratory Animal Center) were housed in an air-conditioned room (23±2°C and 60±10% humidity). Animals received a purified basal diet or a high-cholesterol diet.
containing 1.5% cholesterol and 0.5% cholic acid. The composition of these diets was the same as that reported previously (7). After feeding with each diet for 10 days, the animals were injected with carrageenin or adjuvant. Adjuvant-treated animals were continuously maintained on the same diet given before the injection for 2 or 4 weeks. Each diet was given by pair-feeding to the adjuvant-treated animals, and water was freely available throughout the experiment.

**Induction of carrageenin edema:** Carrageenin edema was induced by injecting 1 mg A-carrageenin (Wako Pure Chemicals) in 0.1 ml saline into the pad of the left hind paw of the rats. The volume of this paw was measured by water displacement just before and at intervals of 1 hr after the injection of carrageenin. Edema formation was assessed as the increased ratio to the paw volume measured before the injection of carrageenin.

**Induction of adjuvant arthritis:** Adjuvant arthritis was induced by a single s.c. injection of 0.1 ml adjuvant, a fine suspension of heat-killed Mycobacterium butyricum (Difco Laboratories) in liquid paraffin at a concentration of 6 mg/ml, into the base of the rat tail.

**Evaluation of arthritis:** The severity of adjuvant-induced arthritis was quantified by paw volume change and an arthritic index. Both hind paw volumes were measured by water displacement to the lateral malleolus (ankle) just before adjuvant injection and then, to follow the development of the inflammatory lesions, at intervals of 3–4 days. The percentage changes in paw volume were calculated as described previously (7). The adjuvant arthritis score was determined by an index described previously (14); the four paws were graded from 0 to 4 based on the periartricular erythema, swelling and ankylosis. The maximum possible score was 16.

**Sampling procedure:** The rats, after overnight fasting, were killed by decapitation on week 2 and 4 after the injection of adjuvant. Those periods correspond to the time for the onset and peak of adjuvant arthritis. The blood was collected into test tubes; then the serum was separated by centrifugation (1500×g for 10 min) and frozen for subsequent study. The spleen, adrenal glands and thymus were excised and weighed.

**Analytical methods:** Total and free cholesterol levels in serum were estimated fluoroenzymatically as described previously (15). Triglycerides were determined by the acetylace tone method of Fletcher (16). Lipid peroxides were spectrofluorometrically determined by the thiobarbituric acid (TBS) method of Yagi (17). Corticosterone was determined by the method of Mattingly (18). Copper was determined spectrophotometrically with the use of bathocuproine (19).

**Statistics:** The results obtained were expressed as the mean±S.E. Student’s t-test for paired observations was used to test for significance.

**Results**

**Effects of dietary cholesterol on carrageenin-induced paw edema:** Figure 1 shows the time curves for the development of the inflammation induced by the injection of carrageenin in rats. There was no significant difference in the degree of the inflammation produced between animals on the basal diet and those on the diet containing 1.5% cholesterol and 0.5% cholic acid. After feeding with each diet for 10 days, the animals were injected with carrageenin or adjuvant. Adjuvant-treated animals were continuously maintained on the same diet given before the injection for 2 or 4 weeks. Each diet was given by pair-feeding to the adjuvant-treated animals, and water was freely available throughout the experiment.

Fig. 1. Effects of dietary cholesterol on carrageenin-induced paw edema in rats. Carrageenin was injected subplantarly to a group of rats on a basal diet (CARR) and a group of rats on a high-cholesterol diet (CARR+CHOL) beginning 10 days before the injection of carrageenin. A dexamethasone-treated group (CARR+DEX) was also included. Dexamethasone (0.3 mg/kg) was given orally 1.5 hr before the injection of carrageenin. Each point represents the mean±S.E. **P<0.01, as compared with the CARR group.
and those on the high-cholesterol diet. On the other hand, dexamethasone, which was administered as a positive control drug, almost completely suppressed the carrageenan-induced edema.

**Effects of dietary cholesterol on adjuvant arthritis:** As shown in Fig. 2, cholesterol feeding significantly suppressed the development of adjuvant arthritis in rats, which was quantified by paw volume change and arthritic score. The suppression was especially remarkable in the early stage of the development of arthritis. By day 17 after the adjuvant injection, the arthritic score of cholesterol-fed rats (ADJ+CHOL) was less than 50% of that of rats treated with adjuvant alone (ADJ).

**Body weight and organ weight changes:** Table 1 shows the body weights and the absolute weights of the thymus, spleen and adrenal glands in rats at week 2 and 4 after the adjuvant injection. All treated animals showed a significant decrease in body weight (23%), marked increases in the spleen and adrenal gland weights (180% and 22%, respectively) and a marked decrease in the thymus weight (46%), compared to the normal control. Cholesterol feeding prevented body weight reduction at week 2 and 4 after the adjuvant injection and also hypertrophy of the spleen and adrenal glands at week 2. Much clearer results were obtained by comparing relative organ weights. At week 4, the relative weight of adrenal glands (31.1±1.4 mg/100 g body wt.) in rats treated with adjuvant plus cholesterol (ADJ+CHOL) was significantly (P<0.01) lower than that (37.5±1.0 mg/100 g body wt.) in rats treated with adjuvant alone (ADJ). Cholesterol feeding had no effect on atrophy of the thymus produced by the injection of adjuvant.

**Lipid levels in serum:** Serum cholesterol and triglyceride levels are given in Table 2. As expected, animals fed the high-cholesterol diet alone (CHOL) showed marked increases (150-200%) in free and esterified cholesterol levels compared to the normal control. These changes of cholesterol levels were further enhanced by the additional treatment with adjuvant at both week 2 and 4 (P<0.01, Group CHOL vs. ADJ+CHOL). In the animals treated with adjuvant alone, marked increases (40-80%) in free cholesterol level were also observed together with consequent

![Fig. 2](image-url). Effects of dietary cholesterol on the development of arthritis in adjuvant-treated rats. Adjuvant was injected subcutaneously into the base of the tail to a group of rats on a basal diet (ADJ) and a group of rats on a high-cholesterol diet (ADJ+CHOL) beginning 10 days before the injection of adjuvant. Arthritis was measured at intervals of 3-4 days after the injection of adjuvant by determining the hind paw volume (A) and arthritis score (B). A control group was given the basal diet alone. Animals of the adjuvant-treated group (n=18) and the control group (n=12) were used, and half of the animals of each group was killed 2 weeks after the injection of adjuvant. Each point represents the mean±S.E. *P<0.05, **P<0.01, as compared with the ADJ group.
Table 1. Effects of dietary cholesterol on body weight and organ weights in adjuvant-treated rats

| Group    | Time after adjuvant injection | No. of rats | Body weight (g) | Thymus (mg) | Spleen (mg) | Adrenal glands (mg) |
|----------|-------------------------------|-------------|-----------------|-------------|-------------|---------------------|
| Control  |                               | 6           | 183±3           | 335±15      | 414±14      | 37.4±0.4            |
| CHOL     | 2 weeks                       | 6           | 175±5           | 276±23      | 428±12      | 36.5±1.2            |
| ADJ      |                               | 9           | 141±2**         | 182±10**    | 1140±60**   | 45.8±1.0**          |
| ADJ+CHOL |                               | 9           | 155±3**##       | 192±15**    | 725±29**##  | 40.7±1.0##          |
| Control  |                               | 6           | 240±3           | 344±18      | 475±6       | 41.7±0.9            |
| CHOL     | 4 weeks                       | 6           | 222±4**         | 289±19      | 495±17      | 38.9±0.1            |
| ADJ      |                               | 9           | 140±3**         | 121±2**     | 827±34**    | 52.3±1.4**          |
| ADJ+CHOL |                               | 9           | 159±5**####     | 108±20**    | 860±47**##  | 49.1±1.3**          |

Adjuvant was injected subcutaneously into the base of the tail to a group of rats on a basal diet (ADJ) and a group of rats on a high-cholesterol diet (ADJ+CHOL) beginning 10 days before the injection of adjuvant. Rats were killed 2 or 4 weeks after the injection of adjuvant. A control group was given the basal diet alone, and a cholesterol-fed control group (CHOL) was given the high-cholesterol diet alone. Each value represents the mean±S.E. *P<0.05, **P<0.01, as compared with the control group. #P<0.05, ##P<0.01, as compared with the ADJ group.

Table 2. Effects of dietary cholesterol on serum lipid levels in adjuvant-treated rats

| Group    | Time after adjuvant injection | No. of rats | Total cholesterol (mg/100 ml) | Free cholesterol (mg/100 ml) | Ester ratio (%) | Triglycerides (mg/100 ml) |
|----------|-------------------------------|-------------|-------------------------------|-----------------------------|-----------------|---------------------------|
| Control  |                               | 6           | 91.6±2.4                      | 13.9±1.0                    | 84.8±0.8        | 146.0±7.0                |
| CHOL     | 2 weeks                       | 6           | 241.6±6.8**                  | 40.3±2.2**                  | 83.2±1.3        | 43.1±2.2**               |
| ADJ      |                               | 9           | 77.7±2.9**                   | 20.0±0.8**                  | 74.2±0.5**      | 72.3±9.5**               |
| ADJ+CHOL |                               | 9           | 458.7±41.2***##              | 90.9±4.5***##              | 79.4±1.6##      | 45.9±5.6##              |
| Control  |                               | 6           | 75.3±3.8                     | 13.0±0.6                    | 82.8±0.4        | 199.8±3.8               |
| CHOL     | 4 weeks                       | 6           | 208.4±6.6**                  | 49.9±5.5**                  | 76.3±1.8*       | 87.4±4.7**              |
| ADJ      |                               | 9           | 86.8±4.0                     | 23.5±1.0**                  | 72.8±0.7**      | 58.5±7.1**              |
| ADJ+CHOL |                               | 9           | 276.5±22.0***##              | 78.5±4.8***##              | 71.5±2.3**      | 36.0±4.5**##            |

Adjuvant was injected subcutaneously into the base of the tail to a group of rats on a basal diet (ADJ) and a group of rats on a high-cholesterol diet (ADJ+CHOL) beginning 10 days before the injection of adjuvant. Rats were killed 2 or 4 weeks after the injection of adjuvant. A control group was given the basal diet alone, and a cholesterol-fed control group (CHOL) was given the high-cholesterol diet alone. Each value represents the mean±S.E. *P<0.05, **P<0.01, as compared with the control group. #P<0.05, ##P<0.01, as compared with the ADJ group.

decreases in ester ratio (EC/TC) at both week 2 and 4. This decrease in the ester ratio was significantly restored by cholesterol feeding at week 2. Serum triglyceride levels were significantly lowered to 30–50% of the control by either cholesterol feeding or adjuvant treatment.

Lipid peroxide levels in serum: As shown in Fig. 3, cholesterol feeding resulted in significant decreases in serum lipid peroxide levels at week 2 (P<0.01, Control vs. CHOL, P<0.05, ADJ vs. ADJ+CHOL) and at week 4 (P<0.01, Control vs. CHOL and ADJ vs. ADJ+CHOL, respectively). Adjuvant treatment also caused a significant decrease (P<0.05), but no synergism due to the combination of these two treatments was observed.

Corticosterone levels in serum: The results given in Fig. 4 show that serum corticosterone levels remarkably increased in adjuvant-treated rats (ADJ) compared to the control at both 2 and 4 weeks by 6.3 times and 7.3 times, respectively. However, cholesterol feeding had no effect on them.

Copper levels in serum: Adjuvant treatment
caused a remarkable increase in the serum copper levels at both week 2 and 4 by 3.1 times and 2.5 times of the control, respectively (Fig. 5). Cholesterol feeding also tended to increase the copper levels except for in the adjuvant-treated animals at week 2.

Correlation between organ weight and inflammatory response: As shown in Fig. 6A, a positive correlation ($P<0.01$) was established between relative adrenal weight and spleen weight in adjuvant-treated animals at week 2. There was a significant correlation ($P<0.01$) even between their absolute weights. However, these correlations were not significant at week 4. The relative adrenal weight was also positively correlated to the arthritis score (Fig. 6B) as well as the logarithmic scale of the percent change of paw volume at week 4 ($P<0.01$, respectively), but not at week 2. Serum corticosterone levels did not correlate with the weight of the organs examined nor the severity of arthritis at both periods.

Discussion

The results presented here demonstrate that dietary cholesterol greatly suppressed adjuvant arthritis, a chronic inflammation, but not carrageenin edema, an acute inflammation. Although the pathogenesis of
adjuvant arthritis is not yet clearly understood, the development of arthritis is considered to be a T-cell mediated delayed-type hypersensitivity reaction to mycobacterial fragments (20, 21). Therefore, the data indicate that cholesterol feeding considerably affects the immune function. Traill and Wick (22) have recently summarized the possible influence of lipids on lymphocyte function. It has also been reported that low density lipoprotein (23) or cholesterol (8-11) may play an important role in modulating the immune response. Our data are consistent with these conclusions.

The present study also shows that dietary cholesterol exerts considerable influence on the changes in organ weight and the substances in serum relevant to the immune response during the development of adjuvant arthritis in rats.

The thymus, spleen and adrenal gland are the organs involved in the immune response. We found that adjuvant injection resulted in severe thymus atrophy, which is a characteristic response to elevated corticosterone level, and severe spleen and adrenal hypertrophy. Persellin et al. (24) have previously observed hypertrophy of the adrenal gland and increased plasma corticosterone concentration in adjuvant arthritic rats. Adrenal corticosteroids can be powerful immune suppressants in rodents. Serum lipoprotein cholesterol has been known as the major substrate for the production of steroid hormone in the adrenal gland (25, 26). Hirai et al. (27) reported increases in adrenal gland weight and adrenal corticosterone level in hypercholesterolemic rats. Therefore, hypercholesterolemia induced by cholesterol feeding may increase the rate of adrenal steroid synthesis and secretion, thus leading to suppression of the immune disease. However, in our study, cholesterol feeding prevented hypertrophy of the adrenal gland in adjuvant arthritic rats. Moreover, it had little influence on the increased serum corticosterone levels. We also observed that the adrenal weight increased with the severity of adjuvant arthritis (Fig. 6B). These results indicate that the suppression of adjuvant arthritis by cholesterol feeding does not result from the increased activity of the adrenal glands, but involves other inhibitory action at sites concerned with the immune response.

The finding that cholesterol feeding caused
suppression of spleen hypertrophy in parallel with the chronic inflammatory response in arthritic rats (Fig. 6) suggests that this is one site of action for cholesterol because the spleen is a major peripheral lymphoid organ and houses proliferating lymphocytes following their stimulation by antigen.

Cholesterol appears to lower the level of the serum lipid peroxide in rats as shown in Fig. 3, as well as in previous studies (7, 28). As lipid peroxides are thought to be one of the aggravating or causative factors of rheumatoid arthritis (29), this cholesterol effect might also be one way in which dietary cholesterol suppresses adjuvant arthritis.

Exogenous copper and copper complexes are known to have anti-inflammatory activity (30). Increased serum copper level has been found in rheumatoid arthritis (31) and in adjuvant arthritic rats (32), providing definitive evidence for the involvement of endogenous copper in inflammatory disease. In this experiment, adjuvant arthritic rats also showed a marked increase in serum copper level, while cholesterol-fed rats tended to have higher levels.

The liver may participate in the homeostatic control of inflammation (33). Bonta proposed that a trigger material released from the injured area stimulates the liver to produce anti-inflammatory substances (endogenous modulators), copper and copper protein, such as ceruloplasmin and superoxide dismutase. On the other hand, liver injury and the resulting decrease of some proteins may improve the inflammatory disease (33). During adjuvant arthritis there is marked impairment of the liver function: a decreased cytochrome P-450 level as well as that of other drug-metabolizing enzymes (34, 35), decreased lipid peroxide synthesis (36), and lower activity of serum lecithin:cholesterol acyltransferase (LCAT) (data not shown), which is of hepatic origin. In these experiments, we found that adjuvant treatment alone elevated the levels of serum cholesterol in rats, at least the free cholesterol, which may have resulted from the decreased LCAT activity. Thus, serum cholesterol may also act as an endogenous modulator in chronic inflammatory response. Studies are continuing to clarify its mechanism of action.

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