Hydrolase Activities in the Rat Aorta

III. Effects of Regular Swimming Activity and Its Cessation

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SUMMARY It is possible that one of the consequences of regular physical activity could be a change in vascular metabolism. We studied the effects of regular swimming activity on specific activities of aortic hydrolases of male rats. Enzymes included: neutral α-glucosidase and lysosomal β-galactosidase, N-acetyl-β-glucosaminidase, cathepsin C, acid α-glucosidase, and acid cholesteryl esterase. After 8 or 16 weeks of a 1-hour/day swimming protocol, specific activities of four of the six aortic enzymes studied were increased over control levels, increases ranging from 7 to more than 42%. Acid cholesteryl esterase was one of the enzymes most affected by the exercise, increasing 25-30% above control levels. An 8-week sedentary period, after 8 weeks of a swimming regimen, resulted in return of the activity of acid cholesteryl esterase, but not those of the other hydrolases, to control levels. Decreases in body weight, blood pressure, and serum lipid levels also occurred in the swimming rats. Weight reduction per se was excluded as an explanation for the increases in aortic enzymes or decrease in serum cholesterol found with swimming. These findings show that regular physical activity is yet another factor with discrete and significant effects on the catabolic activity of vascular tissue.

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VIGOROUS exercise appears to be associated with a reduced prevalence of death from coronary heart disease in man (Paffenberger and Hale, 1975); less extreme exercise has not been so clearly related. Apart from the question of degree of exercise, it remains uncertain whether exercise itself is protective or whether it results in a favorable clustering of other factors associated with reduced risk. Among the latter are a decreased total serum cholesterol level (including decreased low density lipoproteins and increased high density lipoproteins), a decreased serum triglyceride level (Lopez-S et al., 1974; Fletcher and Cantwell, 1974; Wood et al., 1976; Cantwell, 1978), reduced systolic and diastolic blood pressure levels (Scheuer and Tipton, 1977), and increased vital capacity (Kannel, 1967). Similar decreases in serum lipids and blood pressure with swimming or running activity have been described for the rat (Papadopolou et al., 1969; Tipton et al., 1977).

We recently (Wolinsky and Fowler, 1978) have emphasized the importance of understanding the direct effects of putative risk factors for vascular disease on cellular metabolism of the blood vessel wall in addition to noting the levels of certain circulating lipoprotein classes, the blood pressure or blood glucose, to name a few. Ultimately, it is the impact of the risk factor on the vascular tissue that gives rise to manifest vascular disease. Hypertension and diabetes mellitus clearly and directly influence metabolic activity of the vascular smooth muscle cell (Wolinsky et al., 1978a, 1978b). The present study was designed to determine if regular swimming activity influenced cellular metabolism in the rat aorta.

Methods

Male Sprague-Dawley rats (Charles River) were used throughout. Active groups swam 1 hour daily for 8 or 16 weeks in water at 32-35°C. Distribution of eight rats per barrel ensured continuous swimming activity. Sedentary control groups were dipped briefly in water each day at the same time. According to the protocol of Bloor and Leon (1970), rats were housed in pairs and given food and water ad libitum. For monitoring of food consumption, 10 individually caged rats from each experimental group were studied. Dishes and food were weighed every 2 days over several 1-week periods of each study. Body weights and blood pressures were obtained every 2 days over several 1-week periods of each study. Body weights and blood pressures were obtained every 2 weeks following our previous protocols (Wolinsky, 1971; Wolinsky et al., 1978a). Blood pressures were obtained by the tail cuff method on rats lightly anesthetized with ether. Blood for serum lipids was obtained from rats that had been eating ad libitum until they were studied after exsanguination under light ether anesthesia. Rats were routinely killed 20-24 hours after their final exercise period.
Experimental Designs

Sixteen-Week Exercise and Sedentary Return in Young Rats

The experimental design consisted of two consecutive 8-week periods, using 7-week-old rats that weighed 200-225 g at the outset. After the first 8 weeks, two groups of rats, those exercised daily and sedentary controls, were killed. For the second stage of 8 weeks, one-half of the remaining swimmers were maintained on the 1-hour daily swimming protocol, and the others were returned to the sedentary state, with only a brief daily dipping. After a total of 16 weeks had elapsed from the onset of the experiment, three groups were killed: sustained swimmers, sustained sedentary rats, and sedentary former swimmers.

Eight Week Exercise in Older Rats

Two groups of 11-week-old males, weighing 325-350 g at the outset, were exercised for 8 weeks. Age-matched sedentary controls were also studied.

Retardation of Weight Gain in Sedentary Rats

Males, 7 weeks old at the outset, were used. For an 8-week period, individually caged rats in one group had food allocated every 2 days so as to result in a body weight of 80-85% of another group fed ad libitum. This experiment was intended to produce retardation of weight gain comparable to that seen in the swimming rats.

Biochemical Analyses

The aortic segment between the left subclavian and celiac arteries was removed and treated exactly as described in earlier papers (Wolinsky et al., 1978a, 1978b). Each homogenate that was analyzed for enzymes represents intima-media strips of aortas from three rats pooled in 4.5 ml of an 0.25 M sucrose-1 mM EDTA solution. In some experiments, the right kidney and the anterior lobule of the right lobe of the liver were also removed from five rats of each group. Each of these organs from each rat was placed in 10 ml of sucrose-EDTA solution. The tissue then was homogenized with a motor-driven Teflon pestle in a Potter tissue homogenizer (Arthur H. Thomas Co.); 10 strokes over 3 minutes at 4°C gave a well-dispersed homogenate. DNA analyses were done on 1.5-ml aliquots from each homogenate.

Enzyme Analyses

Glycosidases and cathepsin C of aortic homogenates were assayed fluorometrically, exactly as described earlier, with the following exception. After a change in commercial source of the Sprague-Dawley rats used here (Charles River) from those used in earlier studies (Marland Farms), optimal incubation conditions for each enzyme were checked and verified as identical to those of the previous study with the exception that the pH optimum of acid α-glucosidase in the aorta now was found to be 3.6, compared to the previous optimum pH 3.9. Furthermore, in aortas from the strain of Sprague-Dawley rats used here, baseline specific activities of all hydrolytic enzymes studied were consistently higher in controls than those found previously in aortas of another strain (Wolinsky et al., 1978a).

For aortic acid cholesteryl esterase, the same radioisotopic method and assay conditions were used with the exception that the pH optimum of the aortic enzyme in the new rats was found to be shifted slightly to pH 4.5 from the previous optimum pH 4.2. All other requirements for optimal activity were the same as were found previously (Wolinsky et al., 1978a).

The specific activities of neutral α-glucosidase, β-galactosidase, and acid cholesteryl esterase of the kidney and liver tissues were calculated. We previously had determined the optimum pH of these enzymes in both liver and kidney to be identical to those of the aorta and had defined linear conditions of time and protein concentration for each enzyme in each organ.

Under the incubation conditions used, all enzyme activities of aorta, kidney, and liver were linear as a function of time, protein, or DNA concentration. In each experiment, enzymes of each tissue were measured at two dilutions of homogenate to provide an internal control of linearity of activity. Enzyme activities are expressed as milliunits of activity, with 1 mU defined as 1 nmol of substrate hydrolyzed per minute at 37°C. Statistical analyses of results were done with Student's nonpaired t-test when two groups were compared and with Duncan's multiple range test (Duncan, 1955) when three groups were compared. In all cases, a P value of less than 0.05 was considered significant.

Connective Tissue Analysis

In the 8-week experiment in older animals, the thoracic aortic segment, delimited by the left subclavian and celiac arteries, was removed from six rats of the control group and from six rats of the exercise group. Intima-media strips were pooled from each aortic segment; each was analyzed for content of elastin, collagen, and noncollagenous alkali-soluble protein. Details of the chemical procedures used for these analyses are described elsewhere (Wolinsky, 1971). Total weight of each component and its percentage of the original total aortic dry weight were calculated for each vessel and the groups analyzed by Student's nonpaired t-test.

Lipid Analysis

Serum cholesterol was measured by the method of Abell et al. (1952). Serum triglyceride levels were determined by a modification (Van Handel, 1961) of the procedure of Van Handel and Zilversmit.
(1957). In one experiment (data in Table 3), cholesterol and triglyceride concentrations were determined on the Technicon Auto Analyzer II (Manual of Laboratory Operations, 1974). The two cholesterol and triglyceride procedures had been shown previously to give comparable results.

**Morphology and Cytochemistry**

Rings of ascending aorta were removed and incubated for acid phosphatase and N-acetyl-β-glucosaminidase activities, as previously described (Wolinsky et al., 1978a). In addition, histological sections were stained with hematoxylin and eosin or Weigert-van Gieson stains.

**Results**

**Characteristics of the Animal Groups**

Final body and heart weights, blood pressures, serum cholesterol and triglyceride, and total aortic DNA (per three-aorta sample) are shown in Table 1 for rats in the 8-week and 16-week exercise and exercise-sedentary return experiments. Exercise of both durations resulted in significantly lower body weights (P < 0.0001) and significantly higher heart weight-to-body weight ratios (P < 0.001) because heart weight was unchanged. The uniform absence of abdominal fat in the exercised groups may account for the consistent body weight decreases of about 16%. Return to a sedentary life was accompanied by an increased body weight to about 94% of control and the reappearance of body fat.

Mean systolic blood pressure tended to be lower in exercised rats, not quite statistically significant at 8 weeks (0.1 > P > 0.05), but was statistically significant at 16 weeks (P < 0.0001). On return to a sedentary life, blood pressure returned to control levels (P > 0.05).

The same pattern of changes was seen in levels of serum cholesterol and triglycerides. Every group comparison for serum cholesterol showed a significant difference (P < 0.01). For serum triglycerides, the same group trends were seen, but none reached a statistically significant difference. Of interest is the full return of serum cholesterol to baseline values at 16 weeks in the rats returned to a sedentary life. Finally, total DNA was decreased at 8 weeks in the exercised group (P < 0.01) but was not different from control values at 16 week (P > 0.05). We have no explanation for the significantly lower DNA values in the exercised-sedentary rats (P < 0.001).

In the 8-week exercise experiment carried out on older animals (Table 2), very similar group differences were seen, with the exception that the body weight difference was less, but still was statistically significant (P < 0.001). Blood pressure, serum cholesterol and triglycerides, and total DNA all were significantly reduced in the exercised group (P at least < 0.05). In each of the above 8- or 16-week experiments, food monitoring showed no change in normal food consumption by swimming rats. Weight loss that accompanies exercise in these experiments must, therefore, have another explanation; perhaps it simply reflects increased energy expenditure.

The weight-retardation experiment resulted in an average 17% weight reduction (P < 0.001) in the restricted group (Table 3); the mechanism of this weight loss was, of course, different from that responsible for weight loss with exercise. Systolic blood pressures tended to be lower with weight reduction as were aortic DNA values, though both changes were not quite significant (0.1 > P > 0.05). Heart weights were reduced with weight limitation (P < 0.01), resulting in no change in the heart-to-body weight ratio. Note how this differs from all exercise experiments in which the lack of change in heart weight and the increased heart-to-body weight ratios would seem to point to a subtle, but

### Table 1 Characteristics of Rat Groups: Young Rats

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>8-week period</th>
<th>16-week period</th>
<th>16-week period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (15)</td>
<td>Exercise (15)</td>
<td>Control (15)</td>
</tr>
<tr>
<td>Final body wt (g)</td>
<td>443 ± 22</td>
<td>376 ± 24*</td>
<td>541 ± 43</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>116 ± 4</td>
<td>110 ± 12</td>
<td>125 ± 13</td>
</tr>
<tr>
<td>Heart wt (g)</td>
<td>1.37 ± 0.12</td>
<td>1.30 ± 0.08</td>
<td>1.43 ± 0.15</td>
</tr>
<tr>
<td>Heart wt/body wt (%)</td>
<td>0.31 ± 0.03</td>
<td>0.35 ± 0.02*</td>
<td>0.27 ± 0.02</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>63 ± 7</td>
<td>54 ± 4*</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>81 ± 26</td>
<td>63 ± 28</td>
<td>104 ± 34</td>
</tr>
<tr>
<td>Total DNA/3 aortas (μg)</td>
<td>136 ± 11</td>
<td>107 ± 8*</td>
<td>156 ± 5</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. Numbers in parentheses = number of rats.

* P < 0.05 compared to control.

† P < 0.05 compared to exercise.
real, effect of exercise on the heart. Also, unlike the case with exercise, weight limitation did not result in a significant change in serum cholesterol (Table 3). Serum triglycerides, however, were lower ($P < 0.01$), presumably reflecting the decreased food allotment to the weight-limited rats. Our findings of different responses of body composition to caloric restriction and exercise are consistent with the results of others (for review, see Holloszy, 1974).

Biochemical Findings

We have emphasized already that conditions of linearity prevailed for every enzyme examined, but because of its importance (see below), we show the relationship between substrate hydrolyzed and DNA-time product (Bowers et al., 1967) for acid cholesteryl esterase (Fig. 1).

Sixteen-Week Exercise and Sedentary Return Experiments

Figure 2A shows the biochemical findings in pooled aortas of control and exercised groups at the 8-week point. Specific activity (calculated on DNA basis) of four of six hydrolytic enzymes studied was greater in the swimmers’ aortas than in those from sedentary rats. Only $N$-acetyl $\beta$-glucosaminidase and cathepsin C were not significantly changed, but the change in the latter was nearly so. The increases ranged from 19% for acid a-glucosidase to 26% for acid cholesteryl esterase and 42% for neutral a-glucosidase.

Figure 2B summarizes the second 8-week period of the experiment. Control and exercised groups again showed differences for four of the six enzymes studied; cathepsin C is now significantly increased ($P < 0.001$) and neutral $\alpha$-glucosidase not quite ($0.1 > P > 0.05$), with the increases ranging from 7% for acid $\alpha$-glucosidase to 23% for acid cholesteryl esterase. Note that, unlike our previous findings for experimental hypertension or diabetes mellitus, acid cholesterol esterase is one of the enzymes most dramatically affected by exercise. In the exercise group returned to sedentary life, the effects on aortic enzymes were more ambiguous; only acid cholesteryl esterase showed a significant change, with a decrease to control levels.

The changes found in aortic enzymes with exercise were not found in kidneys obtained from these rats. Specific activities of neutral $\alpha$-glucosidase, $\beta$-galactosidase, and acid cholesteryl esterase were
not different in kidneys from control and exercised rats (data not shown).

Eight-Week Exercise in Older Rats

In these rats, specific activities of aortic enzymes showed changes very similar to those just reported (Fig. 3). Four of the six enzymes were significantly increased, with increases ranging from 12% for acid α-glucosidase to 28% for β-galactosidase.

Mixing experiments were carried out to test for the possibility that the increased enzyme activities in aortic homogenates from exercised rats were due to an activator. Table 4 shows specific activities of β-galactosidase after mixing different portions of homogenates from control and exercised rats. The observed activities were very close to those calculated from the original homogenates.

A more detailed study of kidney and liver enzymes was carried out to determine if the aortic changes seen with exercise were similar in those organs, reflecting nonspecific, perhaps weight-related, changes. As shown in Table 5, none of the specific activities of three enzymes measured in homogenates of either organ was significantly different in the control and exercised groups (each P value at least >0.2). Although, unlike the aortic preparation studied, these organs contain multiple cell types, a generalized nonspecific effect of exercise would seem to be excluded as an explanation for the aortic changes.

| Table 4 Enzyme Activity of Mixed Homogenates of Control and Exercised Rat Aortas |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | β-Galactosidase activity (mUt/mg DNA) |
| Proportions*    | Control         | Exercise        | Predicted       | Observed        |
| 0.25            | 0.100           | 0.75            | 35.2            | 36.8            |
| 0.50            | 0.50            | 33.6            | 33.3            |                 |
| 0.75            | 0.25            | 32.0            | 31.7            |                 |
| 1.00            |                 |                 |                 | 30.6            |

* Stated proportions of aortic homogenates from control and exercised rats described in Table 2 were mixed to a final volume of 0.1 ml and incubated with 0.1 ml of substrate. The activities of different mixtures were compared with those calculated from assays performed on original exercise and control homogenates. All observed activities were within the linear range of the assay.

† nmol substrate hydrolysed per minute.
Finally, rats from this experiment were used to determine whether any changes in aortic connective tissue or cell protein that corresponded to changes found in aortic enzymes were present. As shown in Table 6, no significant changes in absolute or relative amounts of these wall components could be detected in length-defined aortic segments. We have not carried out similar studies after longer periods of exercise.

**Weight Retardation Experiment**

Three of the aortic enzymes most changed with exercise were measured in aortas from these rats (neutral α-glucosidase, β-galactosidase, and acid cholesteryl esterase). Restriction of body weight to an average 83% of control values did not influence specific activities of these enzymes in the aorta (data not shown).

**Table 5** DNA Contents and Hydrolase Activities of Rat Kidney and Liver

<table>
<thead>
<tr>
<th></th>
<th>Control (6)</th>
<th>Exercise (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total kidney DNA</td>
<td>3060 ± 200</td>
<td>2850 ± 160</td>
</tr>
<tr>
<td>Specific activities (mU/mg DNA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral α-glucosidase</td>
<td>362 ± 44</td>
<td>339 ± 56</td>
</tr>
<tr>
<td>β-galactosidase</td>
<td>509 ± 85</td>
<td>473 ± 91</td>
</tr>
<tr>
<td>Acid cholesteryl esterase</td>
<td>1.40 ± 0.20</td>
<td>1.42 ± 0.21</td>
</tr>
<tr>
<td>Total liver lobule DNA* (μg)</td>
<td>2290 ± 310</td>
<td>2370 ± 280</td>
</tr>
<tr>
<td>Specific activities (mU/mg DNA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral α-glucosidase</td>
<td>301 ± 40</td>
<td>270 ± 16</td>
</tr>
<tr>
<td>β-galactosidase</td>
<td>190 ± 41</td>
<td>183± 23</td>
</tr>
<tr>
<td>Acid cholesteryl esterase</td>
<td>7.78 ± 0.83</td>
<td>7.85 ± 1.75</td>
</tr>
</tbody>
</table>

Right kidneys and anterior lobules of the right liver lobe from five rats of each group described in Table 2 were studied. Results are expressed as mean ± SD. None of the group comparisons is statistically significant.

* Anterior lobule of right lobe.

**Morphological Findings**

Grossly, aortic walls from exercised rats and those returned to a sedentary life were not different from those of controls. Cytochemical results of incubation of aortic slices for acid phosphatase activity at the 8-week point of the 16-week experiment showed more reactive lysosomes to be present in exercised than in control blood vessels (Fig. 4). At the 16-week point, technical problems associated with the incubation unfortunately prevented satisfactory comparison of control, exercised, and sedentary return groups.

Distention of three vessels from each of the latter three groups with barium-gelatin mixture was done to detect subtle changes in diameter or wall thickness that might not have been appreciated on routine histological sections (Wolinsky, 1971). Other than a slight tendency for cross-sectional areas of...
FIGURE 4 Aortic lysosomes at the 8-week stage of the 16-week exercise experiment. Frozen sections, 10 μm in thickness, incubated for 30 minutes for acid phosphatase activity with β-glycerophosphate as substrate. A: Aorta of sedentary rat. Many tiny lysosomes (arrows) are barely discernible after this brief incubation. B: Aorta of exercised rat. Under the same conditions, large numbers of highly reactive lysosomes (arrows) are demonstrated in smooth muscle cells.

Discussion

Many studies have focused on cardiac changes with exercise but only very few on vascular effects. Coronary artery luminal areas are increased in trained man (Scheuer and Tipton, 1977) and rat (Bloor and Leon, 1970; Froelicher, 1972), and structural adaptation of systemic resistance vessels takes place in the exercised rat (Weiss, 1978). Many but not all studies of the effect of exercise on experimental atherosclerosis show some reduction in disease (Froelicher, 1972). The inconsistency of these latter results serves to highlight the problems of defining exercise vs stress in the experimental situation, particularly where exhausting or awkward activity regimens are employed.

Based on other experimental protocols and their effects on cardiac size and metabolism, the 1 hour/day exercise protocol used here probably can be classified as mild exertion (Froelicher, 1972). Although we cannot state with certainty how swimming activity is perceived by rats, they showed no aversion to the water after a period of training of several days and did not appear to be exhausted by the swimming. Mortality in the swimmers over 16 weeks was less than 10%.

Perhaps the most interesting finding of this study is that, in addition to heart muscle (Scheuer and Tipton, 1977) and skeletal muscle (Holloszy and Booth, 1976), aortic smooth muscle can be considered a tissue that responds to exercise with heightened metabolic activity. It is not yet clear what aspect of exercise is responsible for changes in aortic hydrolytic enzymes. They could reflect hemodynamic forces acting either to produce aortic dilation and increased wall stress, as might occur in a state of increased cardiac output (Scheuer and Tipton, 1977), or to alter endothelial transport function due to high circulating blood flow and increased shear forces (Fry, 1973), thereby increasing vascular permeability. Although experimental hypertension, like exercise, results in increased aortic hydrolytic enzymes, increased blood pressure also leads to increased DNA and increased connective tissue and cellular proteins in the vessel wall (Wolinsky, 1971; Wolinsky et al., 1978b). Not only were these changes not found in the vessels from swimmers, but measured systolic blood pressure actually was lower in swimmers than in controls, making the increased enzymes all the more noteworthy.

The factor associated with swimming that is responsible for the aortic cellular changes found remains unidentified; it could be a change in wall permeability or the level of a circulating hormone. Whatever the ultimate cause, it is remarkable that 1 hour, or less than 5% of the day, devoted to swimming activity influences cellular metabolism in the blood vessel wall over the ensuing 23 hours of sedentary life. Furthermore, we could detect these changes only in the aorta and not in the liver or kidney.

The pattern of response of the hydrolytic enzymes to exercise was different from that seen previously when either hypertension or diabetes mellitus was used as the experimental stimulus. However, it is not possible unequivocally to ascribe the different pattern solely to the type of stimulus used because of the different source of rat used here. The activity of N-acetyl β-glucosaminidase, formerly one of the most responsive enzymes, was not changed with exercise and that of acid cholesteryl esterase, formerly the least responsive enzyme, was most affected by exercise. Indeed, this lipase was the only enzyme to show a clear-cut decrease from an increased level upon return of the rat to a sedentary existence.

In attempting to integrate measured levels of acid cholesteryl esterase in the aorta with measured levels of circulating cholesterol, we found several
interesting patterns. First, coincident with the decrease in circulating cholesterol with exercise, levels of wall enzyme were higher, and the reverse situation was seen when exercise was interrupted and the rats returned to a sedentary state. If circulating lipoproteins are a substrate for the acid cholesteryl esterase, exercise can be considered to have enhanced the calculated "enzyme-substrate ratio." This finding is reminiscent of the situation in experimental diabetes in which circulating levels of cholesterol go up coincident with a decrease in measured aortic levels of acid cholesteryl esterase, thereby markedly reducing the "enzyme-substrate ratio." These alterations could be restored to normal by insulin treatment (Wolinsky et al., 1978a).

If they reflect conditions at the cellular level, considerations of enzyme-substrate balance could have profound implications with respect to potential for lipid accumulation in the blood vessel wall and its cells (deDuve, 1974; Wolinsky and Fowler, 1978).

Although exercise has multiple effects on a variety of clinical risk factors (Fletcher and Cantwell, 1974), on blood fibrinolytic activity (Rosing et al., 1970), on cardiac function and efficiency (Scheuer and Tipton, 1977), as well as on vessel wall metabolism, to name a few categories, it is not yet clear how these are related, if at all, to the atherosclerotic process, or to its clinical sequelae. However, exercise now can be added to a growing list of stimuli that measurably influence hydrolytic enzyme activities of the blood vessel wall. The rapidity and degree of change should heighten our appreciation that vascular tissue is a responsive metabolic organ and increase our awareness of its importance in the complex pathogenesis of vascular disease.

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