

# The Role of the Sympathetic Nervous System in Lipid Deposition.

## I. Increased Lipid Deposits in the Iris of the Sympathectomized Eye in Rabbits Fed an Atherogenic Diet

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**Abstract:**  
*The Role of the Sympathetic Nervous System in Lipid Deposition. I. Increased Lipid Deposits in the Iris of the Sympathectomized Eye in Rabbits Fed an Atherogenic Diet*

■ Rabbits on a high-cholesterol diet deposit more lipid in the iris of the sympathectomized eye.

Histologically, the lipid deposits are composed of sudanophilic staining droplets localized both in smooth muscle cell cytoplasm of the iris dilator muscle and in larger oval cells. Possible metabolic and vascular mechanisms are noted which may underlie these findings. Potential clinical implications of these findings are cited.

**ADDITIONAL KEY WORDS**  
smooth muscle cells

experimental atherosclerosis  
sudanophilic droplets

### Introduction

□ Much interest has focused recently on the important role played by the smooth muscle cell in the pathogenesis of atherosclerosis.<sup>1-7</sup> This is because it is the smooth muscle cell of the intimal and subintimal region which is involved early and to a marked degree by the lipid deposits. It would be no simple matter to isolate these individual smooth muscle cells and to study their metabolism quantitatively under various experimental conditions.

It is known that rabbits on a high-fat diet develop lipid deposits in the eye as well as in various arteries and other sites.<sup>8-10</sup> The iris deposits are strikingly similar to the foam cell lesions observed in atherosclerotic arteries in

humans and experimental animals.<sup>8, 7</sup> The eye provides a model system with three unique advantages: (1) the iris is rich in smooth muscle cells which are well localized; (2) lipid deposits in the eye can be easily seen and their progression can be followed visually; (3) certain experimental modifications can be readily introduced into the model system during life. For example, the eye can be sympathetically denervated. This deprives smooth muscle cells of the levator and iris dilator muscles of locally released norepinephrine. It is increasingly recognized that norepinephrine exerts a regulatory effect on lipid metabolism.<sup>11, 12</sup>

The purpose of the present study is twofold: (1) to document the increased lipid deposition in the iris of the sympathectomized eye in rabbits fed a high-fat diet, and (2) to consider briefly some medical implications of these observations which will be considered fully in subsequent communications.<sup>13, 14</sup>

### Methods

New Zealand white rabbits of either sex with pink irides were used. They averaged ten weeks old.

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TABLE 1

## Representative Ocular Findings in One Litter 131 Days After the Start of the High-Cholesterol Diet

Rabbit number	Cervical sympathectomy	High-fat diet	Sex	Pupil size		Degree of ptosis and enophthalmos	Iris deposits*		Serum cholesterol	Lipid level† Triglycerides
				Normal side	Sympathectomized side		Normal side	Sympathectomized side		
3-0	No (sham)	No	M	8	Same	0	0	0	47	240
3-1	No (sham)	Yes	M	8	Same	0	2+	2+	1640	96
3-2	Yes	Yes	M	7	4	2+	3+	4+	2855	120
3-3	Yes	Yes	F	8	4	3+	4+	4-5+	4870	240
3-4	Yes	Yes	F	7	5	2+	2+	3+	5760	1680
3-5	Yes	Yes	F	8	4	2+	4+	4-5+	3260	90

\*The iris deposits were graded on a scale of 0 to 5+; 5+ represents heavy lipid infiltrates completely enveloping the iris on both sides as well as superiorly and inferiorly.

†These sera were drawn for analysis after the rabbits had been (temporarily) removed from the high-fat diet for two weeks. The values are expressed in mg %.

Eight litters were studied (39 rabbits). The rabbits were housed in individual cages in one indoor, well-lighted room. They were fed either Purina Rabbit Chow ad lib or a high-fat diet ad lib. A given portion of the high-fat diet consisted of 3000 ml of ground Purina Rabbit Chow, 600 ml of olive oil (oleic acid predominating), and 75 ml of cholesterol powder. The composition of this mixture by weight is: rabbit chow 83%, olive oil 16%, cholesterol 1%. After mixing, four liters of water were added. The mixture was then baked at 70°C for 24 hours and cut into small cakes. This diet produced a marked increase in serum cholesterol levels even when sera were drawn in the lipid fasted state (table 1).

Unilateral cervical sympathectomy was performed on either the right or the left side under general anesthesia (Nembutal—15 mg per kg; Sernylan—5 mg per kg). A midcervical incision was made 2 cm lateral to the trachea and extending 2 cm above and below the larynx. The sympathetic trunk was identified within the carotid sheath. It was then stimulated (2 volts) and pupillary dilatation was verified. A 2 cm section of the trunk was then removed. The cut ends of the trunk were tagged with silk for future identification. After suturing, the rabbits were given 600,000 units of Bicillin. In sham operations every step was performed save for trunk transection. Two weeks after operation the animals were started on the control or high-fat diet.

An ophthalmoscope (0 or +12 lens) and a flashlight were used to make serial clinical observations. A deliberate attempt was made to avoid frightening the rabbits so as to avoid pupillary or vasomotor changes related to an excess of circulating catecholamines.

#### LIGHT MICROSCOPY

After sacrifice by decapitation, eyes from selected animals were removed intact, and placed for 24 hours in 10% buffered formalin. Each eye was then divided in half by sagittal section through the vertical meridian. One-half of each eye was embedded in paraffin, sectioned sagittally and stained with hematoxylin and eosin. The other half was washed 24 hours in tap water, oriented for sagittal sectioning and frozen with Tissue Tek embedding medium. Frozen sections were cut at 15 microns and stained with hematoxylin and oil red O to reveal neutral fats. Other eyes were frozen at -30°F for six months before being thawed and photographed (figs. 1-3).

#### ELECTRON MICROSCOPY

Immediately after decapitation, selected eyes were removed intact and opened from behind with four incisions. These extended along the vertical and horizontal meridians from posterior pole to

## SYMPATHECTOMY AND LIPID DEPOSITS

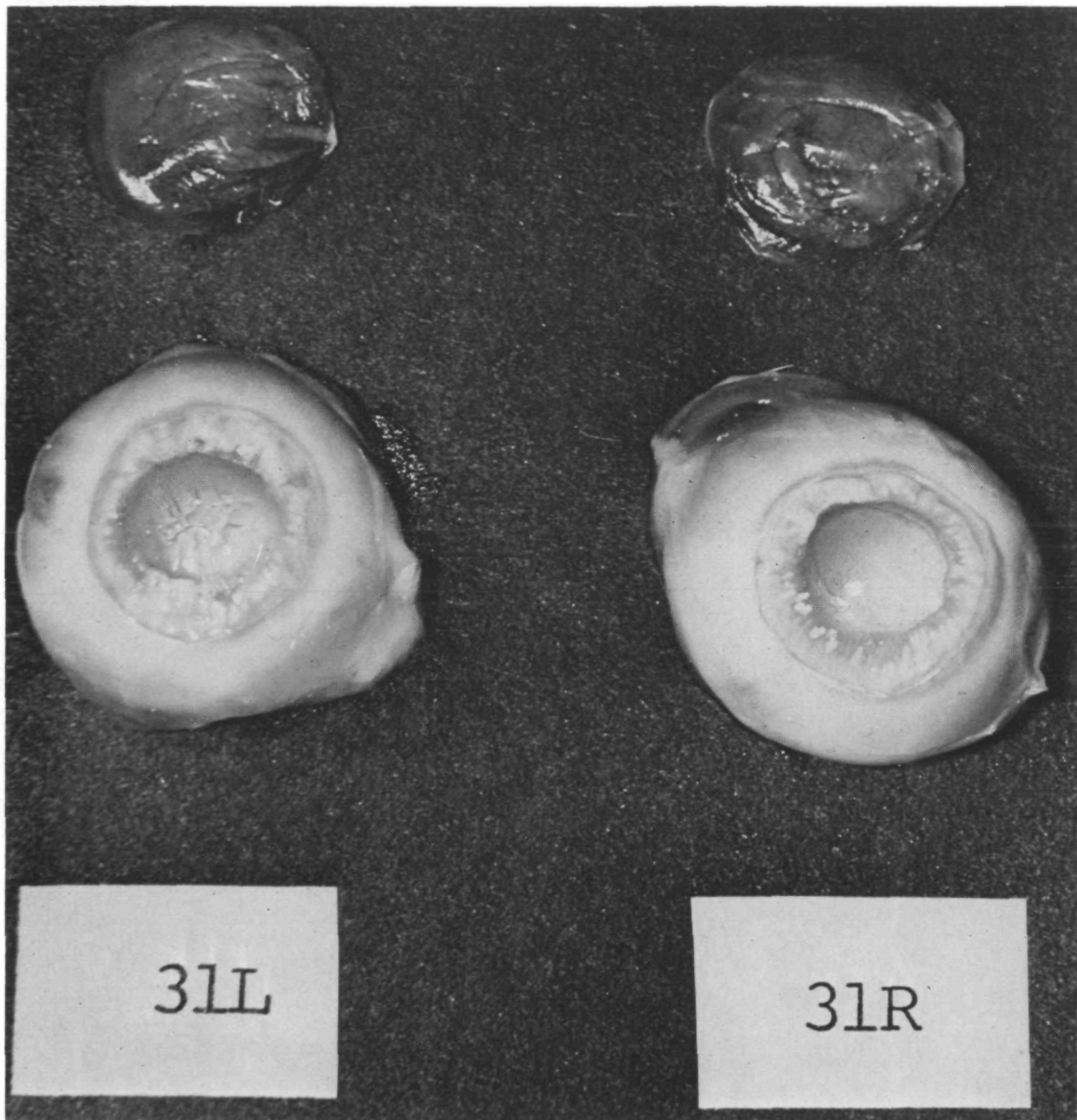


FIGURE 1

*Eyes of rabbit 3-1 in table 1 (left sham operation, atherogenic diet). Note the white, raised, linear to oval deposits. They involve the iris equally on the two sides. The rabbit started the high-fat diet at three months two weeks of age and continued on this diet until death at thirteen and one-half months of age. The corneae are removed.*

anterior pole. The iris-ciliary body complex was dissected free as a unit from the sclera and rapidly placed in 1% phosphate-buffered osmium tetroxide. After three hours' fixation the tissue was washed in phosphate buffer. Small pieces were then removed by radial cuts directed from the iris

root to the pupillary edge. The tissue pieces were dehydrated, embedded in Araldite, and oriented properly for sagittal sectioning. Sections one micron thick were stained with methylene blue-azure II in sodium borate. Thin sections were cut from selected areas, mounted on uncoated copper

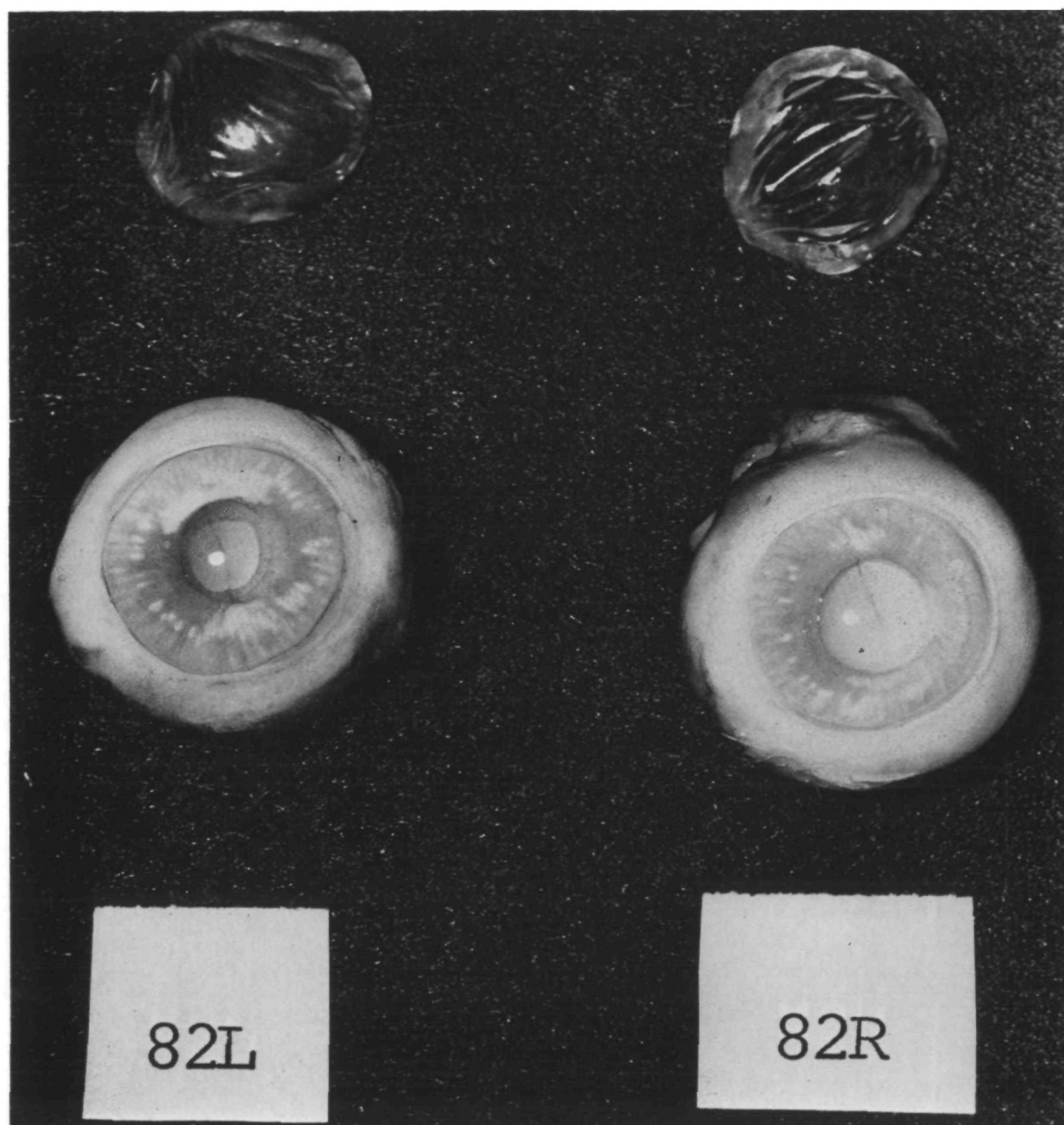


FIGURE 2

*Eyes of a rabbit on the atherogenic diet showing minimal lipid deposits. Note that the heavier, more confluent, white deposits are more evident in the sympathectomized iris (at the viewer's left). This female rabbit started the atherogenic diet at age three months and remained on this diet until death at seven months of age. The corneae are removed.*



## SYMPATHECTOMY AND LIPID DEPOSITS

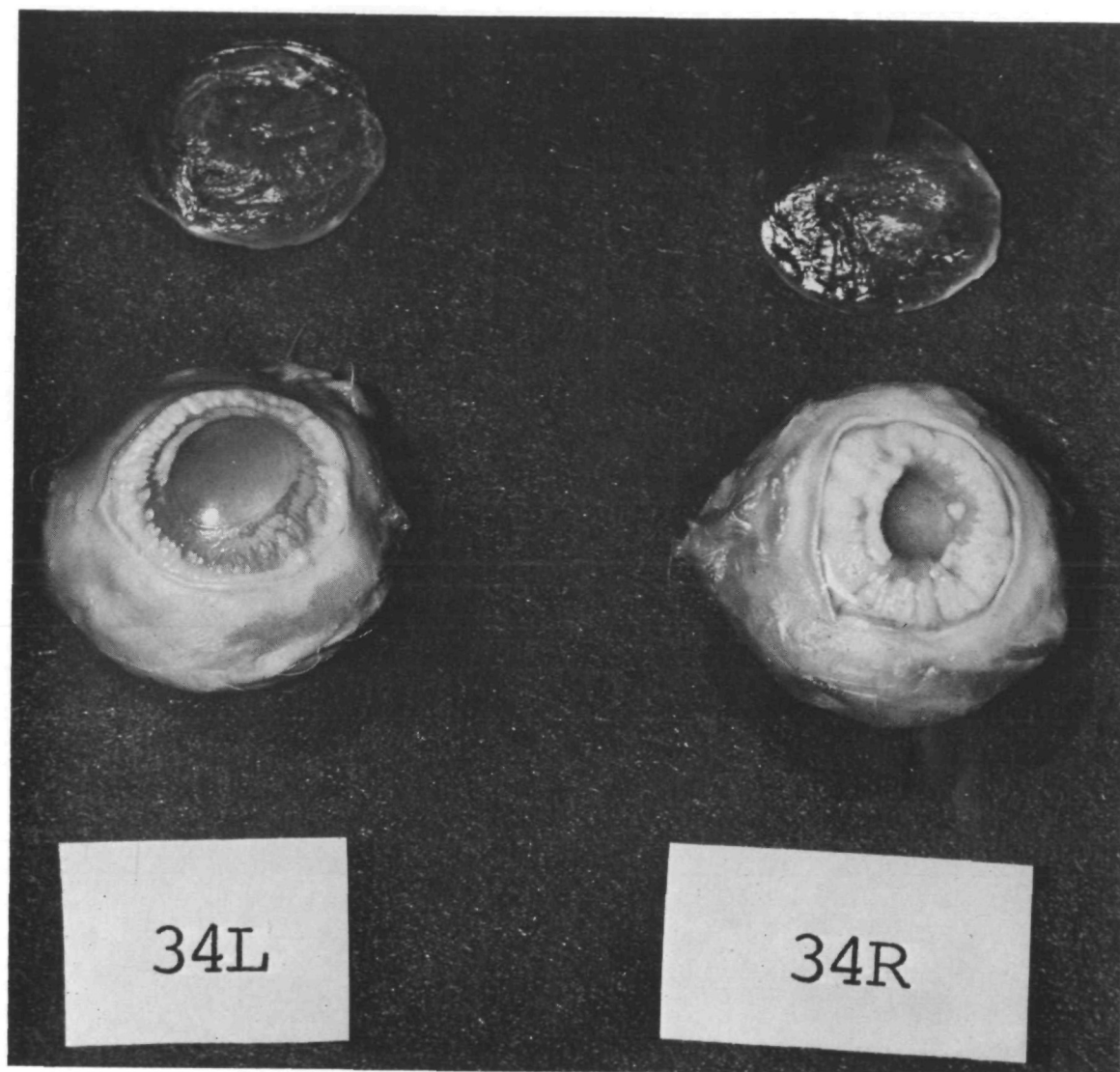


FIGURE 3

*Rabbit eyes showing moderate lipid deposits. Note that the white lipid deposits are more confluent in the sympathectomized iris (at the viewer's right). The rabbit started the atherogenic diet at age three months and continued on this diet until death at 12 months of age. The corneae are removed. The thin white rim on the right margin of the right corneae is a corneoscleral rim plus an adjacent corneal infiltrate (rabbit 3-4 in table 1).*

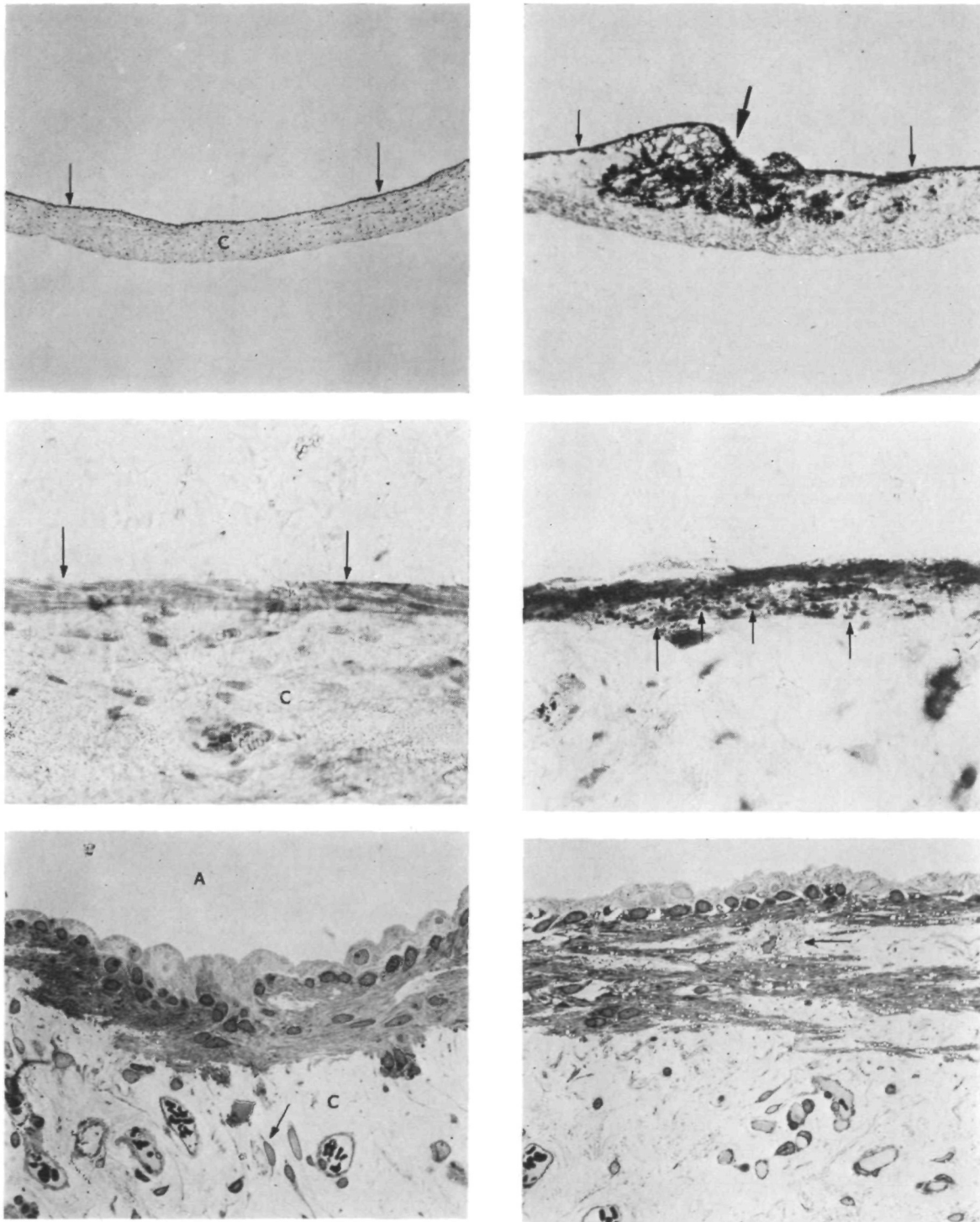
grids, stained with uranyl acetate and lead citrate and examined in a Phillips 300 electron microscope.

### Results

#### CLINICAL FINDINGS IN THE IRIS AND CILIARY BODY

Within eight weeks on the high-fat diet, all rabbits developed raised deposits of whitish

material visible on the surface of the iris. The deposits lined up in radial streaks at three sites of predilection: (1) halfway between the inner and the outer margin of the iris, (2) over the superior and inferior iris at its outer margins (from ten o'clock to two o'clock, and from five o'clock to seven o'clock), and (3) close to the inner margin of the iris near the pupil (more



**FIGURE 4**

*A. Sagittal section of normal iris. The dilator muscle is a thin dark band running along the posterior border of the iris (arrows). Most of the iris consists of con-*

*nective tissue (C) with scattered nuclei throughout. Hematoxylin and eosin,  $\times 50$ .*

*B. Lipid stain of the normal iris. There is no lipid material which stains a brilliant red. The band of dilator*

## SYMPATHECTOMY AND LIPID DEPOSITS

marked superiorly than inferiorly). Sixteen rabbits had the combination of sympathectomy plus the high cholesterol diet. *In every instance, the iris on the sympathectomized side had more deposits.* Representative results in litter three during life are presented in table 1. Representative autopsy findings are illustrated in figures 1 to 3.

The suggestion that the ciliary body was involved by the deposits could be appreciated by the gradual development of a broad circumferential band near the base of the iris which became pinkish white in color. Its density could be appreciated more readily when its outline was backlighted by light which was shined in through the pupil. In advanced stages the entire external surface of the iris became corrugated by confluent, radially arranged heavy lipid deposits (fig. 2).

### VASCULAR CHANGES

The pink iris of the sympathectomized eye took on a slightly more diffuse dusky blue shade than did the intact iris. This subtle finding was

invariably present before lipid deposits themselves obliterated the color differences. This evidence of increased vascularity was seen immediately after sympathectomy and did not represent a pigment change.

There was no consistent evidence that the basic *radial* distribution of the lipid deposits was related to single, visible, radially distributed blood vessels. However, in early stages on the high-fat diet, there was a suggestion that certain *circumferential* vessels occasionally seen on the external surface of the iris did have a faint white sheath.

Some externally visible vessels were very slightly larger in diameter, more numerous and more tortuous in the sympathectomized eye. These changes were more evident in three loci: (1) over the outer margin of the sclera near the corneoscleral junction. Here, the increased vascularity was always much more evident superiorly than inferiorly. (2) Over the inner third of the iris closest to the pupil. Here, a darker network of minute vascular arcades stood out against the lighter pink of the backlighted iris. (3) In somewhat larger single vessels coursing irregularly (usually circumferentially) over the external surface of the iris.

The evidence of greater vascularity in discrete externally visible vessels was present on the sympathectomized side in more than 80% of the rabbits. In general, the findings appeared more evident in rabbits on a normal diet and did not appear to lessen in degree with time. However, the increased vascularity in rabbits on the high-fat diet did tend to become less evident with time.

### CLINICAL FINDINGS IN THE CORNEAE

Lipid deposits became visible in the corneae eight weeks after the iris deposits began. These corneal deposits appeared to be of two types as viewed externally. For descriptive purpose, we referred to one type as a "corneoscleral rim." This dense deposit occurred at the corneoscleral junction at one or more sites. It had a definite innermost edge which frequently gave the appearance of being slightly raised, although it could not be lifted from the cornea with fine forceps.

The second type of corneal deposit was a more hazy infiltration of the cornea. Grossly, this appeared to be localized somewhat deeper than the corneoscleral rim. Its hazy inner border tended to expand inward as a semicircle

*smooth muscle is faintly basophilic (arrows). Connective tissue nuclei in iris stroma (C) are seen. The thickness of the section precludes a distinct focus on some cellular elements. Oil red O and hematoxylin,  $\times 500$ .*

*C. Normal iris in thick section (1 micron). Cellular detail is preserved by buffered osmium fixation. At top, pale epithelial cells form the layer in contact with aqueous humor. (A) Darker cells of the iris dilator muscle reside between these cells and the iris stroma (C). Individual smooth muscle cells have complex cytoplasmic interdigitations. Fibroblasts within the stroma are thin and tapered at one or both ends (arrow). Azure II—methylene blue,  $\times 500$ .*

*D. Rabbit iris after seven months on the atherogenic diet. There is an intense red staining band consistent with neutral fats within the smooth muscle layer (small arrows). A large focal accumulation of intensely red material also protrudes from the posterior portion of the iris stroma (large arrow). Oil red O and hematoxylin,  $\times 50$ .*

*E. Higher magnification of figure 4d. The iris dilator muscle is heavily infiltrated with brilliant red material. This consists of single droplets in areas of favorable focus (arrows). Oil red O and hematoxylin,  $\times 500$ .*

*F. Rabbit iris after seven months on the atherogenic diet. Smooth muscle cells show a striking accumulation of vacuoles. A large vacuole-filled cell is seen next to the muscle layer (arrow). No changes are seen in the epithelial cells or in the elements of the iris stroma. Azure II—methylene blue,  $\times 500$ .*



toward the pupil at one or more sites. A very fine vascular network could be seen within this deposit by slit-lamp microscopy. The corneal deposits showed no necessarily consistent pattern between the two sides. Moreover, *even in the absence of sympathectomy*, the corneal deposits varied somewhat in density and extent from side to side.

#### FUNDUSCOPIC EXAMINATIONS

Rabbits on the atherogenic diet tended to show a faint yellowish sheathing vaguely outlining the retinal vessels. This was difficult to document photographically because the media were somewhat more opaque in the animals which were on the high-fat diet for more than six months. The two sides showed no consistent differences.

#### LIGHT MICROSCOPIC FINDINGS

Irides of rabbits on the atherogenic diet for three and one-half months and seven months were studied in greatest detail. Pathological changes closely paralleled the clinical observations. The denervated iris was the more severely affected; all changes were greater in rabbits on the diet longest. Rabbits on the normal diet showed none of the abnormalities described below.

The most striking findings were minute, clear vacuoles filling the cytoplasm of dilator smooth muscle cells which are located in a band along the posterior border of the iris (compare figures 4c and 4f). Some smooth muscle cells were heavily vacuolated; others had only rare vacuoles. The neutral fat stain showed many droplets lying in a corresponding location within the band of dilator smooth muscle (fig. 4e). Some portions of the iris appeared thickened (compare figs. 4a and 4d). These same areas contained many *large oval cells* filled with vacuoles and osmiophilic bodies (fig. 5). Corresponding accumulations of material staining positive for neutral fat were also found in the same regions, suggesting that these cells were filled with lipid (fig. 4d). Most of the large oval cells were found either in clusters or singly among the smooth muscle cells. Others lay free in normal-appearing iris stroma (fig. 4f, and 5). Although some of these foam cells appeared to cluster around capillaries, smaller clusters of three to five cells occurred in areas far removed from capillaries. The precise localization of the origin of these

foam cells is not simple in a tissue which has as many capillaries as the iris. In some instances foam cell clusters extended from the iris stroma and disrupted the continuity of the smooth muscle layer. Scattered among these large, lipid rich cells were small droplets of neutral fat-staining material which appeared to be extracellular.

#### ELECTRON MICROSCOPIC FINDINGS

The iris smooth muscle cells contained many abnormal vacuoles which had no limiting membrane (fig. 6). These corresponded to the vacuoles and to the oil red O positive deposits seen by light microscopy (figs. 4e and 4f). The smooth muscle cells appeared otherwise normal.

The large oval cells contained many empty vacuoles among which were found normal intracellular organelles (fig. 7). These cells appeared similar regardless of location in the iris stroma or among muscle cells.

No intermediate cells were seen in the material examined thus far. Therefore, it is not yet clear whether some of the large vacuole-packed cells represent a separate cell population or whether some have, in fact, arisen from the iris smooth muscle cells.

#### Discussion

The chief interest of these findings lies in their demonstration that sympathectomy increases the lipid deposition in the iris. The findings confirm, in the eye, the earlier somewhat-

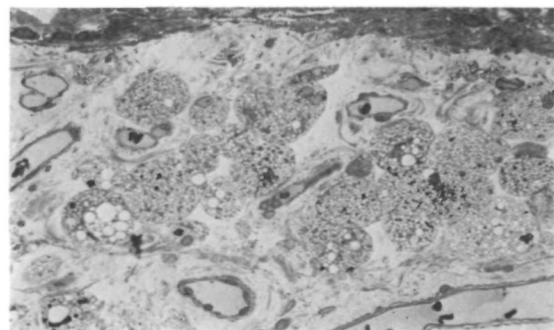
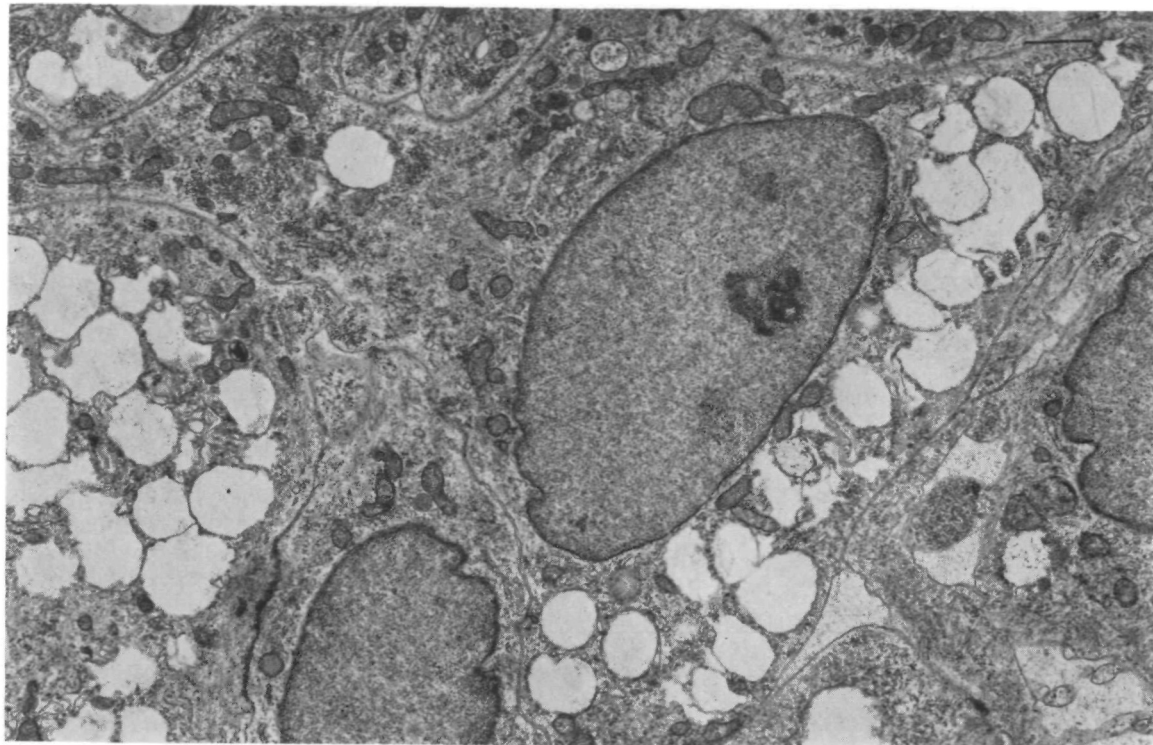


FIGURE 5

*Same iris as in figure 4f. Iris stroma contains clusters of large oval cells packed with many vacuoles and dense bodies. Some of these foam cells appear to accumulate around capillaries. Others do not. Overlying smooth muscle cells also contain vacuoles. Azure II—methylene blue,  $\times 500$ .*



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**FIGURE 6**

*Same rabbit as in figure 4f. Several typical smooth muscle cells of the iris dilator are seen. Vacuoles filling the cytoplasm are empty or contain a scant amount of delicate osmophilic material. The vacuoles do not possess a limiting membrane. The nuclei and subcellular constituents appear within normal limits. The marker indicates one micron.*

neglected observation of Murphy et al.<sup>15</sup> that bilateral lumbar sympathectomy in rabbits increases the sudanophilic lipid deposited in the lumbar aorta. Our findings, like those of Roscoe and Vogel,<sup>16</sup> indicate that corneal lipid deposits are variable and that they do not necessarily run a parallel course with those in the iris and aorta.

Two relatively straightforward mechanisms suggest themselves as hypotheses to explain the present findings in the iris: (1) a metabolic mechanism could be based on the premise that sympathectomy causes a local reduction in norepinephrine, and that this in turn might cause an increase in those lipids, the normal breakdown of which is aided by norepinephrine (norepinephrine induced lipolysis); (2) a vascular mechanism could be based on the premise that vasodilatation, occurring after sympathectomy, permits the flow of more blood rich in lipid and that more

lipid is deposited as a result. The two mechanisms are not mutually exclusive, and still other mechanisms may be in operation as well. Studies currently in progress to clarify these points will be reported in subsequent communications.<sup>13, 14</sup> The following brief comments are pertinent.

### **METABOLIC FACTORS**

Cutting the sympathetic fibers which innervate brown fat causes a local accumulation of lipid<sup>11</sup> and of glycogen. This metabolic effect is attributable to decreased lipid breakdown rather than to accelerated synthesis.<sup>11</sup> Norepinephrine is known to cause an increase in triglyceride breakdown.<sup>12</sup> In addition, our own studies of the denervated iris show that norepinephrine exerts a significant effect on cholesterol ester breakdown. Thus, cholesterol esterase activity is greatly reduced (to only 37% of normal) ten months after unilateral sympathectomy. The triglyceride lipase activity

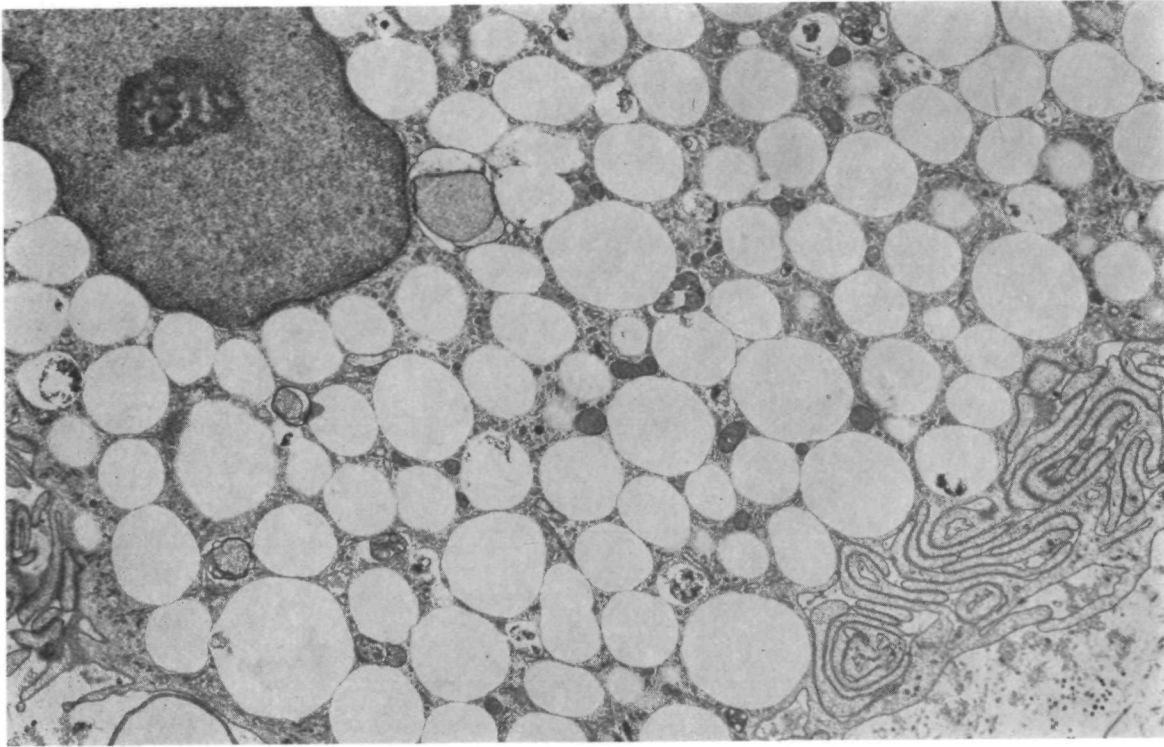


FIGURE 7

*Electron micrograph of a typical large cell as noted in figure 5. The vacuoles have no limiting membranes. There are some unusual dense bodies and membranous figures as well as normal cytoplasmic constituents. The nucleus contains dense chromatin material and some vacuoles indent its limiting membrane. At lower right, the cytoplasmic membrane is thrown into complex narrow interdigitating folds. Same magnification as in figure 6.*

is reduced to a lesser degree (to 62% of normal). Each activity is promptly restored to at least normal levels by the addition of only  $10^{-8}$ M norepinephrine to the assay system.<sup>13</sup> Sympathectomy decreases the uptake of circulating norepinephrine by the sympathectomized eye,<sup>17</sup> and this factor may further reduce the norepinephrine content of the denervated iris.

#### VASCULAR FACTORS

Langworthy and Ortega<sup>18</sup> noted histologically that vessels dilate in the sympathetically denervated rabbit iris. Our rabbits showed this finding clinically. Still, there was no consistent, one-to-one anatomical relationship between the presence of *visible* blood vessels and their involvement by lipid deposits. Rosell's work suggests that the *normal* effect of sympathetic stimulation is to make the capillaries of adipose tissue more permeable.<sup>10</sup> However, if

this were the sole action of sympathetic nerves to the iris, then sympathectomy might be expected to make capillaries *less* permeable and might cause less lipid to be deposited in the iris. Quite the reverse is observed in our studies.

#### RELATIONSHIP OF THE PRESENT FINDINGS TO ATHEROSCLEROSIS

The iris is a useful model because the lipid deposits which develop in the iris closely parallel the development of atherosclerotic lesions in rabbit aorta.<sup>16</sup> Moreover, as observed herein, *smooth muscle cells* of the iris are filled with lipid deposits, and it is lipid deposits in smooth muscle cells which are a prominent early step in the evolution of atherosclerosis.<sup>1-7</sup> Rabbits fed cholesterol reach a higher percentage of sphingomyelin both in the iris and in the atherosclerotic aorta than is present in plasma.<sup>20</sup> These data indicate that all the sphin-



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gomyelin in the iris and the aorta is not accounted for by lipid infiltrating the tissues from the plasma, and thus suggest that local independent metabolic mechanisms may also contribute to atheromatous deposits. Blood vessel walls have the enzymic capacity to produce large amounts of norepinephrine.<sup>21</sup> This, by diffusion, could affect lipid metabolism locally.

Clinical investigators, aware of the impact of sympathectomy on this animal model, might find it appropriate to make long-term observations of the effects of sympathetic denervation in man in hyperlipemic states. The following are illustrative of the kinds of questions which might arise in hyperlipemic states. For example, would an increase in lipid deposits ultimately lessen the benefits of surgical sympathectomies done: (1) for the relief of occlusive disease in various arteries?, (2) for the relief of angina pectoris?, and (3) of necessity, whenever an innervated segment of artery is replaced by a graft? Might the sympathetic lesions which spontaneously occur in the course of diabetes mellitus further contribute to the atherogenic deposits? Are there any untoward long-term effects of adrenergic blocking agents in the presence of hyperlipemia? These questions would seem to require further study.

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