First, I want to say that I am very happy and very proud to be the recipient of the Friedenwald Award, and I am deeply grateful to the research scientists of our association for this high honor. I have accepted this award recognizing that you have made me the delegate of my teachers, colleagues, and students with whom I have collaborated and with whom I share the pleasure of this occasion.

I did not know Jonas Friedenwald, as did several of my more fortunate colleagues. During my education and training, however, I frequently reflected on his extraordinary talent. During 30 years of research, Friedenwald demonstrated a love and an unmatched skill for chemistry and histochemy, mathematics, optics, and physics. He developed new knowledge for the pathophysiology of ocular disease with methods from several disciplines. Yet, he was never too busy to attend to the demands of his patients. His concern for their problems must have reminded him of the dependence of the physician upon his knowledge of biologic mechanisms. We treasure that knowledge for its own sake, but often the stimulus for investigating a particular problem comes from the beleaguered patient. Dr.

Friedenwald frequently turned his attention to glaucoma. Indeed, his theories and contributions to aqueous humor dynamics continue to pervade current research efforts. One among many of his beliefs was that the cause of some forms of glaucoma was a derangement of a local regulatory mechanism. Friedenwald recognized that the adrenergic system might have a regulatory role in the dynamics of aqueous humor formation because drugs in the adrenergic class could influence the steady-state level of intraocular pressure. At one time, experimental studies that he conducted suggested that there existed a humoral activator for the secretion of aqueous humor by the ciliary processes. He found that epinephrine was a potential activator of the oxidative interaction in ciliary body between stroma and epithelial cells, where he believed it furnished a link in that part of the redox chain that lay between the oxidase system of the epithelium and interstitial mediators of the stroma. A search for regulatory mechanisms in the maintenance of intraocular pressure continues to constitute one of the major approaches in glaucoma.

The adrenergic nervous system has certainly been one place to look. It consists of peripheral neurons and chromaffin tissue. The system subserves general body homeostasis and local functions. An example of homeostasis might be the proper distribution of circulating blood to required sites. An example of a local function might be participation in the regulation of pupillary size in relation to visual acuity. In both instances the adrenergic neurons constitute a final common path of a complex behavior pattern. The adrenergic neurons function in two ways. First, they directly control many and various effector tissues by release of norepinephrine.

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Second, they indirectly prevent the unwanted effects from circulating catecholamines. This occurs particularly in densely innervated tissue by an efficient uptake and removal mechanism. Thus, for example, in the iris and nictitating membrane, densely innervated structures, there is but little influence by circulating catecholamines. On the other hand, blood vessels constituting the arterial system, are influenced both by direct innervation and by circulating neurohumors. Finally, in sparsely innervated structures, access to effector cells exists. One expects them to be sensitive to circulating catecholamines and, if appropriately located as in the case of the trabecular meshwork and ciliary processes, to topically applied catecholamines.

The reduction in intraocular pressure after topical adrenergics, as well as other considerations including Dr. Friedenwald’s observations, led to studies of the adrenergic nervous system. In 1955 Linner and Prijot, using the technique of surgical denervation of the sympathetic supply to the eye, were the first to study the influence of the adrenergic nervous system upon steady-state levels of intraocular pressure. They demonstrated that an ipsilateral decrease in intraocular pressure occurs 24 hr after cervical sympathetic ganglionectomy in rabbits. Perfusion experiments indicated that increased outflow of aqueous humor accounted for the decrease in intraocular pressure. The hypothesis was made that the increase in outflow was caused by a release of norepinephrine into the anterior chamber from degenerating nerve terminals in the iris. The transient nature of the ganglionectomy effect—its persistence after death, but its disappearance 30 min later—supported the idea that the responsible agent was released into the anterior chamber and then was either metabolized or washed away. The persistence of the resis-

Table I. Adrenergic blockade and depletion of outflow facility, 24 hr after right ganglionectomy

<table>
<thead>
<tr>
<th>Blockade</th>
<th>Facility (μl/min, mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE</td>
<td>LE</td>
</tr>
<tr>
<td>Ganglionectomy alone</td>
<td>0.62</td>
</tr>
<tr>
<td>α Blockade</td>
<td>0.29</td>
</tr>
<tr>
<td>Reserpine</td>
<td>0.30</td>
</tr>
<tr>
<td>AMPYtyrosinet</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Ten animals in each group; standard error of 0.01 facility units or less.

1Alpha-methyl-para-tyrosine.
The results of exogenous administration of adrenergic effectors strengthen the argument for pharmacologic adrenergic effects upon the outflow of aqueous humor. Let us look at epinephrine. Epinephrine administered topically to the rabbit eye causes an early vasoconstriction and mydriasis and a decrease in intraocular pressure that persists more than 5 hr. The decrease in pressure persists after alpha effects have disappeared; that is, the eye is no longer white from vasoconstriction, and mydriasis is gone. This prolonged decrease in intraocular pressure can be accounted for by increased outflow of aqueous humor and parallels the persistence of cyclic AMP in the aqueous humor. In vitro studies of trabecular tissue have shown that after stimulus with catecholamines the production of cyclic AMP occurs at an increased rate, and cyclic AMP can be found in the incubation media. Finally, intracameral injections of cyclic AMP at $10^{-4}$M or of epinephrine at $10^{-5}$M (final molar concentrations in the anterior chamber) produce a 50% increase in outflow in rabbits and monkeys. A search for the cell of reception has been made and reviewed, but current evidence cannot distinguish among the trabecular cells, en-
dothelia of Schlemm's canal, or ciliary smooth muscle cells as receptor sites for adrenergic stimulation.

A comparison of the response of the outflow channels to adrenergic agents administered exogenously in denervated and normally innervated eyes suggests that endogenous norepinephrine released into the anterior chamber, under ordinary circumstances, is efficiently inactivated by the mechanism of reuptake and binding by the iridic adrenergic nerves. Thus a trabecular effect on outflow resistance from even low doses of norepinephrine delivered into a denervated eye by intracameral injection is assured. As little as 10 ng of norepinephrine base, corresponding to $2.5 \times 10^{-5}$M in the anterior chamber, is active. In the normally innervated eye, however, a final concentration of $10^{-5}$M is required to produce any decrease in resistance. Thus the response is greatly limited by the presence of a normal innervation. Similar results are found after stimulation of the cervical sympathetic nerve. The efficient reuptake mechanism prevents the depletion of iridic stores and thwarts the detection of neurohumor in the anterior chamber and of any change in outflow resistance. On the other hand, if the animal is first treated with cocaine, the neurohumor can be found in the aqueous and an increase in outflow occurs.11

Another problem in the analysis of adrenergic effects on outflow, from a regulatory viewpoint, is the puzzling late progressive effect of exogenously applied adrenergics to increase outflow.12 It is known that in the rabbit the meshwork is coated with a mucinous material, hyaluronidase-sensitive hyaluronic acid. In man, perhaps the same or other mucin exists. Such coating provides resistance to outflow. Experiments done in the...
Fig. 4. Effect on outflow facility of intravenously administered reserpine compared with that of unilateral cervical ganglionectomy. Release of norepinephrine into anterior chamber with each method produces 2.5-fold increase in outflow. (From Rosser, M. J., and Sears, M. L.: J. Pharmacol. Exp. Ther. 164:280, 1968.)

Fig. 5. Progressive increases in outflow facility of aqueous humor after intracameral injection of norepinephrine bitartrate plotted as difference in increase between control (saline) solution and test in 10 bilaterally sympathectomized denervated rabbits.

Aorta of rabbits indicate that epinephrine may decrease the production of mucoid substances. Similar effects in the trabecular meshwork could in time decrease the resistance to outflow. This pharmacologic phenomenon cannot be considered "regulatory" for outflow. Although we have seen that adrenergic tone is of some importance for the facility of aqueous outflow and have learned what is a mechanism for the action of exogenous epinephrine, this puzzling late effect of epinephrine taken together with the obser-
Fig. 6 Time course of the effects of topical epinephrine. Pupil size (○—○) is expressed as the mean ± S.E.M. The decrease in intraocular pressure (Δ—Δ) is expressed as the mean ± S.E.M. of the difference between two eyes of the same animal. Aqueous humor cyclic AMP (x—x) is expressed as the mean percent increase over the control eye (seven animals). (From Neufeld, A. H., Jampol, L. M., and Sears, M. L.: Exp. Eye Res. 14:242, 1972.)

vation that pharmacologic doses of catecholamines are required to produce changes in outflow indicate that other sources of evidence for endogenous adrenergic regulation of intraocular pressure may need to be obtained.

The rate of aqueous humor formation undoubtedly sets the equilibrium level of intraocular pressure. It is determined by the rate of supply of materials to the secretory ciliary epithelia and is probably influenced by hormonal stimulation or suppression of the secretory process. Changes in intraocular pressure during pregnancy and the menstrual cycle and circadian rhythms are among clinical observations suggesting hormonal influences. Information about regulatory mechanisms involving specific hormone-receptor interaction can yield important clues for the discovery of mediators and protein receptors within cell membranes. Furthermore, receptor abnormalities are likely to be involved in a number of pathologic states.

Whether humoral activators of the secretory process can function independently of vasomotor influences on the ciliary capillaries or independently of osmotic forces is a question that surprisingly is still under investigation. The problem is not easily solved because of the difficulty in disentangling vascular effects on aqueous humor formation from the formation process itself. In the intact eye the techniques for measuring formation of aqueous humor are severely limited, demanding high technical skill to assure minimal disturbance of the eye. There is the usual requirement of intraocular cannulation for the purposes of perfusion and manometry. A complex accounting of the net movement of aqueous humor is necessary. Estimates of the formation of aqueous humor from manometric measurements of gross facility are approximate. An analysis must include the components of gross facility, true facility, and "pseudofacility," the pressure-sensitive part of aqueous formation (ultrafiltration) that appears as a facility in formulae for aqueous flow. When laborious photofluorimetric techniques are used to determine aqueous formation, values for the total turnover of fluorescein in the anterior chamber should
include estimates of flow out of the anterior chamber by uveoscleral paths.\textsuperscript{14} Other techniques are useful but have different limitations.

Isolated preparations of ciliary processes were made years ago and again more recently.\textsuperscript{15} In this way vascular and other indirect effects on secretion are eliminated. Planimetric measurements of photographs of optical sections of the processes may permit an estimate of the rate of shrinkage of the processes. Shrinkage is assumed to be a measure of transport across the processes. Another approach to the preparation of the isolated ciliary processes has been to study the uptake and accumulation of substances by these processes.\textsuperscript{16} Here it is hoped that the accumulation of substances by the ciliary processes in vitro represents secretion of these substances that occurs in vivo. A start has been made, but data for the analysis of mediator-receptor mechanisms from these studies are insufficient.

The absence of nerves within the epithelial cell layers of the ciliary processes indicates that they are probably not under direct neural control,\textsuperscript{17} but neurohumoral influences are still probably at work. One way neurohumoral influences work is to affect the rate of synthesis of proteins, including enzymes. Until recently, kinetic analyses of hormone receptor function have been based on the assumption that the number of receptor sites per target cell is constant or that its fluctuations are of little physiological consequence, so that what really matters is the number of hormone molecules that are available for interaction with receptor sites. It is now clear that the number of receptors per cell can vary to influence the response of the target cell to the hormone. Thus a hormone can modulate the cellular level of its own receptor or that of another hormone. Hormonal modulation of hormone-receptor level may have physiologic importance. When one hormone controls the level of receptors for another, the "sensitization" of receptors by steroids and other hormones becomes fascinating. Changes in turnover of membrane receptor molecules in systems other than the eye have already been shown to be influenced by circadian rhythms that may correlate with the level of a particular hormone. There is an in vitro counterpart. In the toad bladder, for example, an innovative technique has been used to identify membrane proteins responding to hormonal activation. Membrane proteins on the mucosal side of the epithelium that extend out from the apical membranes are labeled as the cell is stimulated by an agonist hormone. Increased turnover of such membrane proteins occurs, and the label is used to identify them. These labeled proteins are probably the ones responsible for changes in the permeability of the membrane.\textsuperscript{18} Similar concepts have not yet been applied to ocular tissues.

Changing membrane permeability is a second important mechanism by which hormones can act. Adenyl cyclase is an enzyme in the plasma membrane of the cell. In most cells cyclic AMP is formed at the inner surface of the cell. (See Stryer\textsuperscript{19} for a discussion of cyclic AMP mechanisms.) The rate and locus of formation are suitable for control by hormones, the first messenger. The alteration in the intracellular concentration of cyclic AMP, the second messenger, changes metabolic behavior of the cell, in this case, membrane permeability. The type of response to a particular hormone is thus determined not by cyclic AMP but by the very specific hormone-receptor interaction of adenyl cyclase.

Cyclic AMP plays a critical role in the action of many hormones (e.g., epinephrine, glucagon, and thyroxine) by serving as a second messenger inside the target cell. Such hormones bind to specific receptors on the plasma membrane of the target cell and stimulate adenyl cyclase.

Hormonal activation of adenyl cyclase has been studied in the epithelia of many organs, including the renal tubule and the toad bladder. In the mucosal epithelium of the toad bladder, for example, antidiuretic hormone from the bloodstream interacts with a "receptor," adenyl cyclase, on the serosal surface of the mucosal epithelium and thereby stimulates production of cyclic AMP. Cyclic AMP then diffuses across the cell to the inner surface of the apical membrane and causes a
change in membrane permeability. The state of phosphorylation of a specific membrane protein is probably responsible for the observed changes in permeability of the membrane to sodium or water, or both.20

In this regard, let us consider the ciliary processes. The ciliary processes are composed of blood vessels embedded in a loose connective tissue. The capillaries in this loose stroma are fenestrated, like those in the kidney. Amazingly, in this gland, there is a double layer of epithelial cells, the outer pigmented and inner nonpigmented. During embryogenesis of the ciliary processes the invagination of the optic cup causes these two cell layers to become apposed apex to apex. The pigmented cells represent the forward continuation of the retinal pigment epithelium. The nonpigmented cells represent the forward continuation of the sensory retina.

Electron microscopic studies show that processes of the pigmented cells indent the characteristically thin, fenestrated walls of...
the capillaries. There is an elaborate interdigitation between the adjacent surfaces of the pigmented and the nonpigmented cells, which leads to a relatively firm union between the cell layers. Furthermore, interdigitation of cells may occur, so that the intercellular clefts between the two cell layers are not lined up. Thus, to reach the posterior chamber of the eye, a substance that could pass between the cells of the outer layer may be required to pass through the cells of the inner layer. Extensive lateral interdigitations of this metabolically more active inner cell layer could represent the delivery site in the posterior chamber for a primary secretate.

The first step in the formation of aqueous is the development of a plasma filtrate in the stroma of the ciliary processes. It is upon this stromal pool that the epithelia perform their work. Movement of ions and water through the ciliary epithelia may well be mediated by adrenergic receptors. There are no alpha-activated glands in the body, but adenyl cyclase, stimulated by beta-adrenergic compounds, is very likely involved. Hormonal activation may take place at the basal membrane of pigment cell layer wherein the membrane-bound enzyme catalyzes the intracellular production of cyclic AMP at an increased rate. Cyclic AMP diffuses toward the apical cell membrane. Changes in permeability of that membrane, or of the apposed apical membranes of the two epithelial layers, known to be bridged by gap junctions, may raise or lower the rate of movement of sodium into the region of lateral interdigitations within the nonpigmented cells. Here resides the NaK ATPase pump. Here the secretate may be deposited in the posterior chamber. There are a variety of other hypotheses to consider, and there are many unknowns. The double cell layer introduces complications. Consideration, of course, will also need to be given to the role of the outward-bound anion pump in the ciliary processes.

Evidence for adrenergic regulation of the ciliary epithelia is beginning to accumulate. Using a washed particulate fraction of homogenates of rabbit ciliary processes, Dr. Gregory and Dr. Bausher are out to characterize the cyclic nucleotide system in the ciliary epithelia to determine what role it may play in the regulation of aqueous secretion and membrane permeability. They are systematically carrying forward investigations that, as far as I know, were begun by Waitzman and Woods. They have made considerable progress in establishing evidence for the five-component cyclic AMP-regulated system and have, in addition, looked for a possible role for guanylyl cyclase.

Gregory and Bausher have done a careful kinetic study of adenyl cyclase activity in their preparation and have begun to characterize the activities of the enzyme. As might be expected, the particulate fraction is maximally stimulated by beta-active catecholamines. Guanylyl cyclase activity has been found at about one-half that of adenylyl cyclase. Its role has not been completely worked out. These investigators also found cyclic AMP phosphodiesterase, with about two times as much activity as adenylyl cyclase in the particulate fraction and about 20 times as much in the (3,000 × g centrifugation) supernatant. Two kinetically distinct cyclic AMP phosphodiesterases have been found. Regulators are being sought in all instances.

Could vasopressin be one of the regulators? Within recent years an enormous amount of information has been learned about the antidiuretic hormone. The synthesis of vasopressin takes place in the nerve bodies of the supraoptic and paraventricular nuclei. The molecules are stored in terminal bodies of their axons and released primarily by the stimuli of hypertonicity and volume depletion. The receptors for vasopressin actions are in the renal collecting ducts, and the result of their activation is rapid reabsorption of water. In vivo the system is activated and inactivated rapidly in response to brief changes in hydration.

The pharmacologic effects of vasopressin on intraocular pressure in vivo and on isolated ciliary body in vitro that have been reported have been impressive. Endogenously released vasopressin already has a target for its action, i.e., the cells of the renal collecting ducts. Furthermore, its action is quick to increase cell membrane permeabil-

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Fig. 9. Structure of timolol, (−)-1-tert-butylamino-3-(4-morpholin-1,2,5-thiadiazol-3-yloxy)-2-propanol hydrogen maleate.

Fig. 10. Effects of a single dose of timolol (MK) to decrease intraocular pressure (ordinate, mm Hg) is compared over a time span of 270 min with the effects of single doses of propranolol (PR), norepinephrine (NE), isoproterenol (I), acetazolamide (A), and epinephrine (E) in 12 rabbit eyes whose outflow facility was largely impaired by an inflammatory reaction after an injection of alphachymotrypsin done more than two months prior to testing. The average intraocular pressure in these eyes was 31 mm Hg.22

ity probably via cyclic AMP, and then quickly off. Although the state of body hydration, both directly via osmotic forces and indirectly via the hormone vasopressin, definitely would affect the volume of the globe, it seems unlikely that aqueous humor formation would be a specific target for the whim of vasopressin. Confirming this impression, Dr. Gregory has found that the adenylate cyclase in his preparation of ciliary epithelia is insensitive to vasopressin. Other mediators and regulators will be sought.

When a hormone activating the suppression or formation of aqueous humor finally is found and evidence for its action finally established, it is likely that there will be a specific receptor on the plasma membrane of the ciliary epithelial cells that will initiate the events leading to a change in the rate of aqueous humor secretion. Steps will then be
taken to isolate the membrane receptor. Dr. Moshe Lahav, a former member and research affiliate of our department, together with his colleagues in Jerusalem, have reported the utility of a fluorescent beta-adrenergic blocker, 9-aminoacridin propranolol, to study beta receptor sites in rat ocular beta-adrenergic receptors. Recently developed techniques permit direct identification of binding sites in membranes that may have many of the physiologic characteristics to be expected on the beta-adrenergic receptor binding cells. These techniques generally use radioactively labeled beta-adrenergic antagonists such as (−[3H] dihydroalprenolol, (±)[125I] hydroxybenzylpindolol, and (±)[3H]propranolol. Dr. Neufeld of our department reported an initial attempt to identify adrenergic binding sites in a crude preparation of several and various ocular membranes. Detailed stepwise chemical analysis of receptors and receptor hormone interaction will be required. After recognizing the hormone, a receptor transmits its information to other molecules within the cell. Binding studies of labeled hormone and a correlation between binding and known characteristic responses are some of the steps. The molecular identification of the receptor will be difficult. Finally, we must learn how to relate hormone binding to the receptor sites of physiologic activity for a given hormone. These problems are not insurmountable; however, they will require the skill and care of serious-minded chemists.

Although the search for a hormone activator proceeds, model systems based on molecular concepts have already been developed in the search for new drugs. Many of these relied on the realization that several kinds of hormone receptors on the surfaces of cells are linked to the plasma membrane-associated enzyme adenylate cyclase. For example, catecholamine-responsive cyclases from heart or lung may represent functional beta-adrenergic receptor complexes. They have been used to identify agonists or antagonists. Dopamine-responsive cyclases from specific areas of the brain can be used to screen for antipsychotic agents. Recently in ophthalmology, the drug timolol, a potent beta-adrenergic antagonist, was commercially synthesized and studied. In 1974 Dr. Silverstone and co-workers in our laboratory had the opportunity and good fortune to show that timolol produced impressive reductions in intraocular pressure in rabbit eyes whose outflow was largely impaired after an intraocular injection of alphachymotrypsin. After these animal studies, human investigations were permitted and conducted. The decrease in aqueous humor formation produced by timolol will be a mechanism that clinicians can use in the treatment of human glaucoma. Reports attest to the effectiveness of the drug. Thus the molecular approach to specific hormone-receptor interaction in regulatory studies of intraocular pressure can yield important information for the discovery of mediator and receptor proteins and may have a therapeutic product as well.
We want to know what are the glaucoma genes and to learn their abnormal products. Regulatory studies may eventually reveal abnormal mediator or receptor proteins, but other approaches can be used. It is known that mutagens can produce a genetic alteration in a quantity or quality of protein. Very little use of this technique has been made in vision research. In 1957 Jensen and Matson did report that chickens reared from hatching under continuous incandescent illumination developed shallow anterior chambers and increased intraocular pressure within the first month of life. It is doubtful that the elevation of intraocular pressure was accompanied by an open chamber angle mechanism; nevertheless, the experiments do point out that an environmental agent produced abnormal structural characteristics. The nature of the abnormal structural protein and control mechanisms for its production may be worthy of study. Certainly, if this model is not utilized, the technique can be exploited in the development of other models.

But other approaches to look for the "glaucoma protein" or "proteins" are required. Screening aqueous humor to look for accumulated or missing metabolites or an abnormal metabolite can be considered a presumptuous approach. It is a step that, if successful, would require an enormous amount of luck. Direct assay of an enzyme from tissue biopsy could be attempted.
If a structural abnormality does exist in a protein variant, the detection of that protein variant might better be approached by culture of normal and abnormal ocular tissue and cells. François et al. have looked at the production of mucopolysaccharides by a culture line of trabecular cells. Recently in our laboratory Dr. Yamashita has been studying the ciliary epithelium and has shown the regenerative ability of the nonpigmented cells after injury. These observations give us renewed confidence that we can grow and harvest these cells, as well as trabecular cells. After radioactive labeling of proteins in a cell line undergoing active biosynthesis, determination of proteins can be done with the aid of gel electrophoresis. Working with Ted Reid in our laboratory are Sam Pahuja and Dale Gregerson who have modified a two-dimensional gel electrophoresis system and are making plans to examine the protein constituents of normal and abnormal ocular tissues. By a determination of the positions and quantities of labeled proteins on these gels, it may be possible to identify abnormal proteins or differences in the metabolism of proteins from abnormal ocular tissues. Depending on the quantity of material available, these techniques can be coupled to immunologic procedures in order to identify differences among proteins.

A serious collaborative commitment to organ, tissue, and cell culture of normal and glaucoma eyes must be made in an effort to learn more about the actual protein constituents of these tissues. The techniques are available. The problem now only seems to be an organizational commitment to their solution.

Now I have come to the end of my report. I have told you a little bit about what our research group has done, what it is currently doing, and what we plan for the future. There are good problems to be solved. In many instances the techniques are available. Where they are not, I have confidence that they can be developed.

Off and on during the preparation of this paper I have tried to think of a phrase that best describes the impact of Dr. Friedenwald's work upon the research effort in vision and ophthalmology that is being carried forward by the membership of this organization. Perhaps it is a line from the funeral oration of Pericles that most appropriately tells of Friedenwald's place. "The whole earth is the
sepulchre of famous men; and their story is not graven only on stone over the native earth, but lives on far away, without visible symbol, woven into the stuff of other men’s lives.”

I thank you again for this high honor.

Various parts of the work accomplished and reported in this lecture were done in collaboration with many friends and colleagues in ophthalmology. Among them are Professor Ernst Bárány, Larry Bausher, David Dueker, Susan Fenn, Douglas Gaasterland, Doug Gregory, Lee Jampol, Vic Jocson, Katsuyoshi Mizuno, Arthur Neufeld, Shozo Nishida, Ted Reid, Marvin Rosser, Truman Sherk, Yoshihiko Shiode, David Silverstone, Torgeir Vegge, Hideaki Yamashita, and the two mountain boys pictured at the lecture were David and Jon Sears.

This manuscript was completed during National Secretary’s Week with unflagging energy and skill by Mrs. Susan Fleischmann!

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