It is the purpose of this review to discuss the effects of cardiovascular renal agents as they may relate to ophthalmic practice. While the drugs in general are grouped according to their major therapeutic use, I should like to emphasize within this framework, first, those which are used by the ophthalmologist in the treatment of ocular disease; second, those which may have an effect on the eye, but which are not primarily used in the treatment of ocular disease; and, third, the toxicity which may result from either the systemic use of agents employed for ocular conditions or the combination of these with cardiovascular renal drugs which the patient is taking for other reasons. Particularly the latter deserves mention. Often the patient presents with multiple vials of pills he is taking. It is the responsibility of the ophthalmologist who may place this patient on some systemic medication to be certain that this does not produce additive effects which may be toxic.

**Antihypertensive agents**

The past decade and a half has seen the synthesis of many antiarterial hypertensive agents as well as the isolation of the active principles of certain natural products. Table I by no means lists all the agents which have been developed, nor is the classification necessarily descriptive of the mode of action of the drug. Particularly this is true of the first and third groupings.

Under the first classification, that of drugs acting at or near peripheral nerve endings, we are dealing with a variety of agents which have quite different modes of action. I have included, for its historic interest, Dibenamine, an example of adrenergic blocking agents, which, incidentally, are no longer in favor in the treatment of hypertension. Dibenamine was the first of its type made available for study, and second it was the first of the systemic agents, excluding the osmotic agents, which enjoyed at least some temporary success in the treatment of glaucoma. Christensen

From the Department of Ophthalmology, University of Minnesota Medical School, Minneapolis, Minn.
Table I. Some antihypertensive agents in current use

I. Act at peripheral nerve endings
   - Dibenamine (not in use)
   - Guanethidine (Ismelin)
   - Bretylium tosylate (Darenthin)
   - Reserpine
   - Alpha methyldopa (Aldomet)
   - Pargyline HCl (Eutonyl)

II. Ganglion blocking agents
   - Tetraethylammonium chloride (Etamon)
   - Hexamethonium chloride (Bistrium)
   - Pentolinium tartrate (Ansolyse)
   - Mecamylamine (Inversine)

III. Others
   - Hydralazine (Apresoline)
   - Reserpine
   - Veratrum preparations

There are newer drugs which exert a peripheral effect somewhat similar to that of the Rauwolfia derivatives. Among these are guanethidine (Ismelin) and bretylium tosylate (Darenthin). These drugs affect only the sympathetic nervous system and have been found to be of value in the treatment of hypertension. They produce a similar clinical effect, although their modes of action may differ. Thus guanethidine is a norepinephrine depleter whereas bretylium tosylate is not. Of these, guanethidine is of particular interest since it has been shown to lower the intraocular pressure. While it reduces the norepinephrine at the nerve endings and blocks the effect of nerve stimulation, it does not block the action of injected norepinephrine or epinephrine. Indeed, the pressor effect of these agents is actually greater in the animal pretreated with guanethidine. In this respect the action of the drug simulates a surgical sympathectomy.

Guanethidine has been shown to produce a delayed miosis and drop in ocular tension in the rabbit. Our own experience in the laboratory indicated that the drug had no effect on the intraocular pressure of the normal cat when administered topically or injected into the internal maxillary artery. It did produce a drop in the intraocular pressure when injected into the femoral vein but this paralleled the fall in the arterial blood pressure and presumably was caused by it. However, ours were acute experiments. In humans, administered topically either alone or as an adjuvant, it does lower the intraocular pressure in glaucomatous eyes. We were originally quite enthusiastic, but now feel that it offers little improvement over standard forms of topical therapy. There would appear to be no contraindications to the combined uses of any of these agents and the systemic agents which the ophthalmologists might employ.

The enzyme inhibitors present an interesting group of antihypertensives. One group consists of the decarboxylase inhibitors of which the principal one
is alpha methyldopa (Aldomet). It blocks the decarboxylation of aromatic amino acids and consequently reduces the production of catecholamines, including noradrenaline and serotonin. In spite of the good biochemical data and inferences, the exact mechanism by which this enzyme inhibitor influences hypertension is not known. Alpha methyldopa has been tested for possible ocular hypotensive action with both topical and systemic routes of administration and has been found to have little or no effect. There would appear to be no contraindication to the combined use of this agent and those which an ophthalmologist might employ.

An even more interesting example of enzyme inhibition of arterial hypertension is that of the inhibitors of monoamine oxidase. The enzyme itself sometimes has been regarded as the one responsible for the inactivation of epinephrine and norepinephrine. This does not seem to be the case. The inhibitors of this enzyme, of which pargyline HCl (Eutonyl) is an example, cause postural hypotension. They seem to exert their effect by preventing the release of norepinephrine at sympathetic nerve endings in a manner which is not understood and, indeed, may not even be related to the inhibition of the enzyme.

The ganglion blocking agents have been fairly extensively employed. They are potent hypotensive agents. These drugs block both parasympathetic and sympathetic ganglia and thus have the unwanted side effect of blocking the parasympathetic nervous system. This would appear to account for one of the undesirable side effects of these agents, i.e., blurring of vision, an effect, incidentally, which is reported to be blocked by pilocarpine. They have been reported to lower the intraocular pressure. Presumably this is due to the drop in blood pressure but this cannot be stated with certainty. Their use for this purpose would certainly be infrequent. The only instance might be in an acute glaucomatous eye when other therapy has failed. It is of interest to note that certain cases of blindness have resulted from a too profound depression of the systemic blood pressure by these drugs, usually at surgery. Their mixture with agents that ophthalmologists might use should produce no harmful additive effects.

The other drugs have varied sites of action. The effect of hydralazine, once thought to be central, is now considered to be directly on the smooth muscle of the arterioles. The effect of the veratrum derivatives has been shown to be on the baroreceptors and chemoreceptors of the carotid sinus, the aortic arch, etc. These drugs have no use in the treatment of ocular disorders, although presumably they would lower the intraocular pressure by virtue of their effect on the blood pressure. There is no contraindication to their use in the treatment of ophthalmic disorders.

Before leaving the antihypertensive agents, I would like to consider the question of arterial hypertensive crises which the ophthalmologist may encounter. Very rarely is it necessary for the ophthalmologist to treat these conditions, but, occasionally, particularly postsurgically, a hypertensive crisis may result that requires treatment. There is a variety of agents that might be used for this purpose. These have largely been covered by Gifford. We have preferred reserpine, giving it generally intravenously although intramuscular injection is probably just as adequate. Reserpine does not reduce the blood pressure as rapidly as many of the other agents. Thus, readministration of this drug, if a more profound effect is desired, should be delayed for one to two hours, lest the patient suffer too great a drop in blood pressure.

Perhaps a more commonly encountered condition is the hypotensive crisis. This usually presents to the ophthalmologist when the patient arrives at the operating room and may be the result of the preoperative medications. The usual supportive therapy is indicated of course. There are a number of agents which can be given intravenously or even intramuscularly for
Table II. Diuretics

<table>
<thead>
<tr>
<th>Organic mercurials</th>
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<tbody>
<tr>
<td>Carbonic anhydrase inhibitors</td>
</tr>
<tr>
<td>Benzothiadiazines</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
</tr>
<tr>
<td>Osmotic agents</td>
</tr>
</tbody>
</table>

Table III. Organic mercurials

<table>
<thead>
<tr>
<th>Chlormerodrin (Neohydrin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercalluride (Mercuhydrin)</td>
</tr>
<tr>
<td>Mercaptomerin sodium (Thiomerin)</td>
</tr>
<tr>
<td>Mercumatin (Comeritin)</td>
</tr>
<tr>
<td>Merethoylline (Mercuzerthin)</td>
</tr>
<tr>
<td>Merethoxylline (Dicurin)</td>
</tr>
<tr>
<td>Mersalyl and theophylline (Salyrgan)</td>
</tr>
</tbody>
</table>

Diuretics

The major groups of diuretics that are presently used are listed in Table II. The listing is not complete. The organic mercurials (Table III) have been used with consistent success in instances where diuretics are indicated. Presumably the diuretics poison an enzyme of the kidney tubules which is necessary for the reabsorption of sodium chloride from the glomerular filtrate. The diuretic induces both sodium and chloride excretion. There may be a slightly greater excretion of chloride than sodium to the extent that the patient may develop a hypochloremic alkalosis. There is no appreciable diuresis of potassium. The diuretics do not reduce the intraocular pressure and consequently have no value in the treatment of glaucoma. In general, there is no contraindication to the combined use of carbonic anhydrase inhibitors or other agents the ophthalmologists might use and the organic mercurials. Similarly the organic mercurials do not alter the action of the carbonic anhydrase inhibitors on the ciliary epithelium.

Diuretics

This purpose. The drug which we have found most useful has been Aramine in doses of 1 mg., fairly slowly, given intravenously while following the blood pressure of the patient. The dose can be repeated if necessary.

Cardiac glycosides

The exact mechanism by which digitalis and its derivatives stimulate cardiac muscle is not known. These compounds, the cardiac glycosides, have profound effects at the cellular level. Among these is an inhibition of Na-K ATPase. This enzyme mediates the transport of cations across cellular barriers in such a manner that potassium is concentrated within a cell and sodium is excreted from it. The inhibition of the enzyme by the cardiac glycoside results in a depletion of cellular potassium and a gain in cellular sodium. The depletion of potassium from the digitalized heart is well known. It is not intended to imply that the depletion of potassium is responsible for the inotropic action of digitalis.

The ciliary body is among the tissues that contain the enzyme, and it may mediate the transfer of sodium from the plasma to the posterior chamber and thus play a role in the formation of aqueous humor. Certain objections to this view can be raised. Nonetheless, if the view is correct, the cardiac glycosides should inhibit aqueous flow and cause a reduction in ocular tension. This, indeed, has been reported and digoxin has been suggested for use in the treatment of the glaucomas that are resistant to the standard therapeutic methods. Considering the toxicity of the digitals derivatives, this form of therapy for glaucoma does not have much to commend it. The suggested use of digoxin combined with carbonic anhydrase inhibitors should also be approached with caution since the latter promotes potassium diuresis. The digitalized heart is peculiarly sensitive to hypokalemia, cardiac arrhythmias being produced.
Table IV. Various carbonic anhydrase inhibitors of ophthalmic interest

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Mg./tablet</th>
<th>Usual dose/day (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Diamox</td>
<td>250</td>
<td>250-1,000</td>
</tr>
<tr>
<td>Dichlorphenamide</td>
<td>Daranide</td>
<td>50</td>
<td>50-300</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>Naptazane</td>
<td>50</td>
<td>100-400</td>
</tr>
<tr>
<td>Ethozolamide</td>
<td>Cardrase</td>
<td>125</td>
<td>125-500</td>
</tr>
</tbody>
</table>

carbonic anhydrase inhibitors promote the diuresis of sodium with chloride and, in addition, a diuresis of bicarbonate and potassium. The diuresis of bicarbonate causes a drop in the bicarbonate level of the plasma and a systemic acidosis. This ultimately limits the effectiveness of the carbonic anhydrase inhibitors as diuretics. The drugs are thus most valuable in conditions other than those requiring chronic administration of diuretics.

Among these conditions is the treatment of glaucoma, which was originally reported by Becker approximately one decade ago. The compounds available are listed in Table IV. The idea that carbonic anhydrase is involved in the secretion of aqueous fluid was implicit in the theory of aqueous formation advanced by Freidenwald. While the exact mechanism by which the enzyme mediates the formation of aqueous is not known, it has been abundantly proved that the carbonic anhydrase inhibitors exert their ocular hypotensive effect by reducing the rate of aqueous formation. They appear to act directly on the ciliary body. Thus, the hypotensive response does not appear to be due to altered chemistry of the blood or to some other metabolic effect audistance. Multiple studies, both static and dynamic, of the chemical changes induced in the plasma and aqueous of many species by these enzyme inhibitors have been made.

The side effects of the carbonic anhydrase inhibitors are well known (Table V). Generally, in clinically effective dosages, the various carbonic anhydrase inhibitors induce much the same side effects. On occasion it is feasible to switch from one inhibitor to another and reduce the side effects while maintaining effective clinical management of the glaucoma. However, by and large, intolerance to one is also accompanied by intolerance to another in full therapeutic doses. There are certain exceptions to this. The compounds do induce a typical sulfonamide type of skin rash. Upon switching to an agent that has a different structure, e.g., from acetazolamide to dichlorphenamide, the skin may clear and the patient be continued on a carbonic anhydrase inhibitor.

There is one side effect that I think deserves greater emphasis. The carbonic anhydrase inhibitors are kaluretic agents and induce a hypokalemia. Generally, the carbonic anhydrase inhibitors are prescribed
to individuals in the older age group. These patients may also be taking other kaluretic agents, such as the thiazide derivatives or steroids. Such combinations may depress the serum potassium to the extent that the patient may have symptoms of hypokalemia, such as weakness, generalized malaise, gastrointestinal disturbances, and thirst. In addition, if the subject is digitalized, cardiac arrhythmias may develop. The problem is usually solved by adding potassium to the regimen. We generally have preferred potassium bicarbonate, and some have even suggested that this may enhance the effect of the drug on the ciliary epithelium. Potassium chloride can be used.

When the individual is subjected to some stress that might reduce the blood pressure, or if there is a hepatic failure, the amount of circulating aldosterone might increase. This will promote potassium diuresis and further deplete the body stores of potassium. I have been involved in one instance in which the patient became ill of an undiagnosed condition while on both steroids and dichlorphenamide. The case was finally diagnosed pneumonia, but this was done at autopsy. During the course of the illness the serum potassium fell to below 2 mEq. per liter and the bicarbonate to below 5 mEq. per liter. Certainly all of this cannot be attributed to the medications the patient was receiving, but they may have been a factor.

There are few contraindications to the use of the carbonic anhydrase inhibitors. They can be prescribed to patients manifesting fairly severe renal failure. They should be used with circumspection in patients who may have severe electrolyte imbalance, e.g., following prolonged emesis, and should not be used in patients with adrenal failure.

The benzothiadiazine or thiazide derivatives are widely used in medicine. Not only are they diuretics but they seem to have an antiserum hypertensive effect as well. These derivatives promote the excretion of sodium and chloride. They also promote kaluresis. The exact mechanism of the action is not known. They compete with the organic mercurials and to a certain degree also with the carbonic anhydrase inhibitors, but in each instance, however, they have an additional site of action. They, like the organic mercurials can cause the low salt syndrome. Their kaluretic effect is certainly observed in acute administration, however, there is some suggestion that in chronic administration they might not deplete the body potassium appreciably although hypokalemia will persist. When prescribing a carbonic anhydrase inhibitor to a patient who is already receiving one of the thiazide derivatives, it is well to be on the lookout for hypokalemia. I might add that these drugs do not lower intraocular pressure.

I should like to mention in passing one of the newer groups of drugs, namely, the aldosterone antagonists. These are the spirolactones and the compound now available is spironolactone (Aldactone). Aldosterone inhibits the excretion of sodium and promotes potassium diuresis. Spironolactone, therefore, reduces potassium loss and promotes sodium excretion. The drug is effective only in the presence of aldosterone or other steroids having similar action. It appears to be quite effective when used in combination with other diuretics. Spironolactone has been reported to reduce aqueous formation in the rabbit. There would appear to be no contraindication to its use with carbonic anhydrase inhibitors. Indeed, it may be of value since it reduces kaluresis.

The osmotic agents have had a resurgence in ophthalmic therapy, particularly since the studies of Javid on the use of intravenous urea in patients with cerebral edema. Urea readily penetrates the red cell and when used in even hypertonic concentrations causes a hemolysis. Hence, it is administered with some innocuous substance which does not readily penetrate the red cell and thus prevents the hemolysis. It can be given orally but this is somewhat unpalatable and consequently is generally given intravenously as a 30 per
cent solution in 10 per cent fructose, usually in doses of 1 to 1½ Gm. per kilogram administered over a period of 30 to 45 minutes. As such it has a profound ocular hypotensive effect. Urea has its greatest benefit in acute glaucoma where standard methods have failed and in surgical procedures where a particularly soft eye is desired. There are no contraindications to using it in combination with carbonic anhydrase inhibitors. Its use is contraindicated in individuals with severe renal or hepatic dysfunction or in the presence of marked dehydration.

The other agent currently used for similar purposes is a sugar alcohol, mannitol. This has almost three times the molecular weight of urea and because of limitations in its solubility, mannitol does not have the potential for lowering the intraocular pressure that urea has. It is generally administered as a 20 per cent solution (although 25 per cent can be achieved with heating) intravenously in doses of 1 to 2 Gm. per kilogram over a period of 30 to 45 minutes. There are no particular contraindications to its use.

Among the side effects of the osmotic agents are rather severe headache, dizziness, and nausea. An overload of the cardiovascular system is feasible. Urea is irritating to the tissue and may cause phlebitis as well as local irritation if extravasation occurs.

The mechanism of action of these agents is generally considered to be simply osmotic, i.e., increasing the osmotic pressure of the plasma with respect to that of aqueous promotes the movement of water from the eye. However, this may not be the sole effect of urea since we have found in our laboratory that, when administered rapidly, urea may produce a very great rise in the osmotic pressure of the plasma and yet not lower the ocular tension of the cat. Indeed, it may be raised. The exact reason for this is not certain. I simply mean to suggest that there may be an additional mode of action of urea on the intraocular pressure.

The last agent to be discussed in this regard is glycerol, which recently has been reported to be of value in the treatment of glaucoma. It has not been administered intravenously to my knowledge, although this would be feasible providing some sugar or sugar alcohol such as mannitol was given with it. Glycerol enters the red cell very rapidly and can cause hemolysis. However, it can be very valuable when taken orally with fruit juice. Generally, we administer 1 c.c. per kilogram. There is no reason why more could not be used. It is absorbed in the small intestine and does cause a rise in the osmotic pressure of the serum and a drop in the intraocular pressure (Fig. 1). It can be administered at home. The side effects are not marked. Since it is metabolized it does not promote diuresis, and catheterization of the patient is not necessary.

Summary

Of the large number of drugs which come under the classification of cardiovascular renal agents, only a few, the carbonic anhydrase inhibitors and the osmotic diuretics, have general usefulness in ophthalmic practice. However, a good portion of the patients the ophthalmologist may be treating may be taking other cardiovascular
renal drugs for other physical ailments. The drugs of this group most likely to be encountered are the antiarterial hypertensives, the cardiac glycosides, and the various diuretics. Ophthalmologists must recognize the mode of action and side effects of these drugs, and the added toxicity which may be induced by the therapy which he applies.

Cover illustration
Induction of differentiation, long known to embryologists as important in initial embryologic development, is possible even at later times.

Here, in studies by V. Muthukkaruppan, a University of Wisconsin graduate student from India working in the laboratory of Dr. Robert Auerbach, the anterior lens epithelium from advanced mouse embryos has been isolated in tissue culture in combination with mesenchyme and neural retina. In the absence of neural retina, the anterior lens epithelium fails to differentiate. Addition of neural retina leads to induced development of a complete, new lens with oriented lens fibers. Note that the neural retina is separated from the lens epithelium by a thin millipore filter, indicating that some inductive material must pass from the neural retina during the inductive process. (Courtesy of Drs. V. Muthukkaruppan and R. Auerbach.)