When a newborn is exposed to partial pressures of oxygen above the normal blood range, the result may be Retrolental Fibroplasia. Most premature babies who have received oxygen are routinely examinated prior to hospital discharge. Of the more popular mydriatic agents employed, there have been various reports of systemic manifestations. Our study was conducted to confirm previous reports and to find an adequate combination for dilatation without the systemic effects. Our current protocol at United Hospitals Medical Center (UHMC) was included in the study.

MATERIAL AND METHODS

Forty-eight neonates of mixed races were studied during routine dilatation prior to funduscopic examination. In each case, the patient was stable, euthermic, supine, approximately one hour after feeding. Gestational ages, determined by physical and neurological characteristics in conjunction with menstrual history, ranged from 30 to 45 weeks. Present weights were from 1040 to 4350 grams.

Blood pressures were obtained using a cuff with an ultrasound transducer* over the brachial artery. This concept was originally prepared by Ware and Kirby, and its accuracy was documented by Hochberg et al. The cuffs remained in place throughout the entire recording period. Apical heart rates were obtained by auscultation of the precordium. In all cases, heart rates and blood pressures were recorded for three intervals at five minutes apart. An average of these figures provided control levels.

Eye drops were instilled three times: one drop in each eye at five minute intervals. Excess tearing or overflow was wiped away immediately with a clean gauze. Heart rates and blood pressures were recorded at five minute intervals for the first 15 minutes and then every 15 minutes. After one hour, eyelid retractors were applied and pupil sizes were measured with a small, clear plastic ruler. Sizes before and after a high intensity spotlight were noted. Routine funduscopic examination then proceeded.

To eliminate the possibility of subjective variation, the same investigator applied the drops, recorded pressures and heart rates, and measured pupil sizes.

The study was divided into four groups:

Group I: Six neonates ranging from 34 to 40 weeks and weighing from 1530 to 4060 grams comprised this group. They were given an open trial of 10 percent aqueous phenylephrine.

Group II: We subdivided a total of 19 cases into six subgroups. In a double blind fashion, we randomly administered ten percent aqueous phenylephrine, one percent cyclopentolate, one percent tropicamide, and as our control, normal saline. These infants ranged from 32 to 45 weeks and weighed 1040 to 4350 grams.

Group III: A group of 12 infants, with ages from 30 to 42 weeks and weights from 1280 to 2460 grams, received the protocol for dilatation used at UHMC Intensive Care Nursery. This protocol is a combination of drops of 2.5 percent aqueous phenylephrine, one percent cyclopentolate, and one-half percent tropicamide. One drop of each was placed in both eyes and repeated at five-minute intervals for three
instillations, i.e., nine drops in each eye.

Group IV: To facilitate the administration of a combination of drops, our pharmacy prepared a mixed solution. By combining 7 cc of one percent cyclopentolate, 7 cc of one percent tropicamide and .625 cc of ten percent aqueous phenylephrine in a 15 cc dropper bottle, a solution containing one-half percent cyclopentolate, one-half percent tropicamide, and 2.5 percent phenylephrine was prepared. We divided 11 neonates into two subgroups:

Subgroup A—four infants from 36 to 38 weeks and weighing 2200 to 3000 grams received a total of three drops in each eye.

Subgroup B—seven infants from 37 to 44 weeks and weighing 1769 to 3800 grams received just one drop of the solution in each eye.

RESULTS

Group I

Approximately ten minutes following ocular application of 10 percent aqueous phenylephrine, there was blanching of the skin around the eyes in all cases (Fig. 1). The blanching was most intense between 20 and 30 minutes. This phenomenon has been previously reported.5-6

Our data, recorded on Table I and Graph I, shows a consistent but variable rise in blood pressure ranging from 10 to 26 mm Hg systolic and 2 to 14 mm Hg diastolic. The effects on heart rates were variable. In four of the six cases, we observed a drop in heart rate, perhaps explained on the basis of a rise in blood pressure causing a reflex slowing of the heart.7 This is further discussed in the section to follow.

Pupil sizes ranged from 4 to 6 mm (average 5.0 mm) and did not vary with direct light stimulation. It is worth noting that in patients no. 5 and no. 6, both with dark irises, there was minimal dilatation and yet considerable change in blood pressure. The blue-eyed baby, patient no. 2, had a maximum dilatation in this series. This phenomenon has been previously reported by Haddad et al.8

Group II: Double Blind Study.

Subgroup II-A: This series involved three infants who received one percent cyclopentolate. (See Table and Graph II-A.) We observed no significant variation in blood pressure. Patient No. 3 presented an interesting finding in that there was a steady rise in heart rate. This may represent the action of the anticholinergic agent on the heart.9 Maximum dilatation was 5 mm in all three cases; however, in the presence of a high intensity lamp, two of the pupils dropped to 4 mm.

Subgroup II-B: Four patients received 10 percent aqueous phenylephrine in the second series of cases. (See Table and Graph II-B.) Three of the infants developed blanching of the skin around the eyes. Curiously, the 35-week-old, 1860 gram black infant was the exception. In two patients, No. 1 and No. 4, there was a consistent rise in blood pressure. A drop in heart rate was also observed in patient No. 4. Dilatation was from 3.0 to 5.0 mm (average 4.4 mm). Maximum dilatation was observed in the blue-eyed infant. It was interesting to note that there was greater dilatation in the white, though more mature babies.

Subgroup II-C: Group II-C comprised three patients who received our control solution of normal saline. (See Table and Graph II-C.) As expected, pressures and heart rates were stable. There was no dilatation.

Subgroup II-D: This series of three patients received 10 percent viscous phenylephrine. This agent was included in order to compare its effects with the 10 percent aqueous solution. (See Table and Graph II-D.) One of the infants displayed a steady and consistent elevation in blood pressure with an associated fall in heart rate. (Note that the weight of this infant was only 1040 grams.) The other two infants showed no significant variation in pressure or heart rate. Dilatation ranged between 4 and 5 mm (average 4.7 mm) and light reflexes remained active in two of the patients. Blanching occurred on the skin around the eyes in two cases.

Subgroup II-E: Three babies received one
instillations, i.e., nine drops in each eye.

Group IV: To facilitate the administration of a combination of drops, our pharmacy prepared a mixed solution. By combining 7 cc of one percent cyclopentolate, 7 cc of one percent tropicamide and .625 cc of ten percent aqueous phenylephrine in a 15 cc dropper bottle, a solution containing one-half percent cyclopentolate, one-half percent tropicamide, and 2.5 percent phenylephrine was prepared. We divided 11 neonates into two subgroups:

Subgroup A—four infants from 36 to 38 weeks and weighing 2200 to 3000 grams received a total of three drops in each eye. Subgroup B—seven infants from 37 to 44 weeks and weighing 1769 to 3800 grams received just one drop of the solution in each eye.

RESULTS

Group I

Approximately ten minutes following ocular application of 10 percent aqueous phenylephrine, there was blanching of the skin around the eyes in all cases (Fig. 1). The blanching was most intense between 20 and 30 minutes. This phenomenon has been previously reported.1,4

Our data, recorded on Table I and Graph I, shows a consistent but variable rise in blood pressure ranging from 10 to 26 mm Hg systolic and 2 to 14 mm Hg diastolic. The effects on heart rates were variable. In four of the six cases, we observed a drop in heart rate, perhaps explained on the basis of a rise in blood pressure causing a reflex slowing of the heart.7 This is further discussed in the section to follow.

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Group II: Double Blind Study.

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Subgroup II-B: Four patients received 10 percent aqueous phenylephrine in the second series of cases. (See Table and Graph II-B.) Three of the infants developed blanching of the skin around the eyes. Curiously, the 35-week-old, 1860 gram black infant was the exception. In two patients, No. 1 and No. 4, there was a consistent rise in blood pressure. A drop in heart rate was also observed in patient No. 4. Dilatation was from 3.0 to 5.0 mm (average 4.4 mm). Maximum dilatation was observed in the blue-eyed infant. It was interesting to note that there was greater dilatation in the white, though more mature babies.

Subgroup II-C: Group II-C comprised three patients who received our control solution of normal saline. (See Table and Graph II-C.) As expected, pressures and heart rates were stable. There was no dilatation.

Subgroup II-D: This series of three patients received 10 percent viscous phenylephrine. This agent was included in order to compare its effects with the 10 percent aqueous solution. (See Table and Graph II-D.) One of the infants displayed a steady and consistent elevation in blood pressure with an associated fall in heart rate. (Note that the weight of this infant was only 1040 grams.) The other two infants showed no significant variation in pressure or heart rate. Dilatation ranged between 4 and 5 mm (average 4.7 mm) and light reflexes remained active in two of the patients. Blanching occurred on the skin around the eyes in two cases.

Subgroup II-E: Three babies received one
percent tropicamide in this group. (See Table and Graph II-E.) No significant changes were observed. Dilatation ranged from 5 to 5.5 mm (average 5.3 mm).

Subgroup II-F: This series consisted of three babies receiving aqueous phenylephrine. (See Table and Graph II-F.) There were no significant changes in blood pressures or heart rates.

Dilatation ranged from 4 to 5 mm (average 4.5 mm). Two patients retained a response to our light source with a 1 mm change. There was no blanching noted.

Group III

A group of 12 infants received a combination of drops. (See Table and Graph III.) In two of the
infants, there was a rise in both systolic and diastolic blood pressures. One of these was a blue-eyed 33-week-old baby; the other was a 37-week-old oriental with a grey iris. Heart rates did not vary significantly. The dilatation provided was from 7 mm to 8.5 mm (average 7.7 mm). There was no skin blanching.

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**GROUP IV**

This final group of 11 infants received the premixed solution of 2.5 percent phenylephrine, one-half percent cyclopentolate and, one-half percent tropicamide. (See Table and Graph IV-A and B.)

Subgroup A: Three drops were administered
TABLE II-C

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5 MIN. | 68/22 | 44/20 | 38/20|
| 10 MIN. | 68/24 | 48/20 | 44/20|
| 15 MIN. | 74/24 | 42/20 | 42/20|
| 30 MIN. | 68/24 | 46/20 | 38/20|
| 45 MIN. | 74/24 | 44/20 | 42/20|
| 60 MIN. | 74/24 | 46/20 | 38/20|

PUPIL | 2M | 2M | 1M |
PUPIL E LIGHT | 3M | 3M | 2M |

GRAPH II-C

in each eye of four infants at five minute intervals apart. There were no changes in heart rates or blood pressures. At one hour the average dilatation was 7.1 mm.

Subgroup B: This group of seven received just one drop in each eye. There were no changes in heart rates or blood pressures. Average dilatation at one hour was 7.0 mm.

TABLE II-D

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GRAPH II-D

REVIEW OF THE LITERATURE

Phenylephrine: (Neo-Synephrine, Isophrin)

Phenylephrine-HCl (levo-hydroxy-3-methylamino-3-hydroxyethyl-benzene-HCl) was first studied by Barger and Dale in 1910. It was not until 1936 when Health reported its use in ophthalmology. The difference chemically from epinephrine
is that it lacks an OH group at the C-4 of the benzene ring. It is a white crystalline, relatively stable compound, readily soluble in water and alcohol. It has been following chemical structure:²

\[
\begin{array}{c}
\text{Epinephrine} \\
\text{Phenylephrine}
\end{array}
\]

Having almost a pure alpha adrenergic effect, the heart, which contains beta receptors, is not directly stimulated. Mechanism of action is mostly by direct stimulation at the alpha receptor sites. There seems to be some ability to liberate stored nor-epinephrine. The main effects of phenylepinephrine are within the cardiovascular system by contraction of smooth muscle within the walls of arterioles. This vasoconstriction results in an increased pe-
### TABLE III

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<td>8MM</td>
<td>7-1/2MM</td>
</tr>
</tbody>
</table>

**GRAPH III**

- **Systolic Pressure** (CASE #5)
- **Heart Rate**
TABLE IV-A

<table>
<thead>
<tr>
<th>CASE</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>WEEKS</td>
<td>37</td>
<td>36</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>2200</td>
<td>3000</td>
<td>2170</td>
<td>2960</td>
</tr>
<tr>
<td>RACE</td>
<td>White</td>
<td>Oriental</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>IRIS</td>
<td>Blue</td>
<td>Grey</td>
<td>Brown</td>
<td>Brown</td>
</tr>
<tr>
<td>B.P.</td>
<td>H.R.</td>
<td>B.P.</td>
<td>H.R.</td>
<td>B.P.</td>
</tr>
<tr>
<td>CONTROL</td>
<td>52/22</td>
<td>70/30</td>
<td>156</td>
<td>64/28</td>
</tr>
<tr>
<td>5 MIN.</td>
<td>50/24</td>
<td>70/28</td>
<td>156</td>
<td>60/24</td>
</tr>
<tr>
<td>10 MIN.</td>
<td>48/22</td>
<td>70/30</td>
<td>156</td>
<td>74/32</td>
</tr>
<tr>
<td>15 MIN.</td>
<td>54/22</td>
<td>74/32</td>
<td>156</td>
<td>64/30</td>
</tr>
<tr>
<td>30 MIN.</td>
<td>48/22</td>
<td>68/30</td>
<td>152</td>
<td>64/28</td>
</tr>
<tr>
<td>45 MIN.</td>
<td>52/20</td>
<td>72/28</td>
<td>148</td>
<td>64/30</td>
</tr>
<tr>
<td>60 MIN.</td>
<td>54/20</td>
<td>74/26</td>
<td>156</td>
<td>66/24</td>
</tr>
<tr>
<td>PUPIL</td>
<td>7MM</td>
<td>7MM</td>
<td>8MM</td>
<td>6-1/2MM</td>
</tr>
<tr>
<td>E LIGHT</td>
<td>7MM</td>
<td>7MM</td>
<td>8MM</td>
<td>6-1/2MM</td>
</tr>
</tbody>
</table>

When the drug reaches the eye, either via the blood stream or by ocular instillation, it relaxes the sphincter muscle of the iris and strongly contracts the radial muscle fibers. It lowers intraocular pressure by slowing the influx of aqueous humor. If a 10 percent solution is used, there is occasionally light cycloplegia.9,12

In the normal human eye, the effects on pressure and accommodation are slight, if any. However, in patients with open angle glaucoma, it may raise or lower pressure. It may precipitate angle closure glaucoma in patients with narrow anterior angles and shallow anterior chambers.13

Clinical uses of phenylephrine in ophthalmology were described by Heath in 1949. It may
TABLE IV-B

<table>
<thead>
<tr>
<th>CASE</th>
<th>1</th>
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<th>4</th>
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<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEEKS</td>
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<td>43</td>
<td>37</td>
<td>38</td>
<td>40</td>
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<td>3400</td>
<td>1850</td>
<td>1760</td>
<td>2330</td>
<td>3000</td>
<td>3860</td>
</tr>
<tr>
<td>RACE</td>
<td>Black</td>
<td>White</td>
<td>Black</td>
<td>White</td>
<td>White</td>
<td>Spanish</td>
<td></td>
</tr>
</tbody>
</table>

| CONTROL | 78/38 132 | 44/20 144 | 42/20 166 | 62/18 160 | 64/20 160 | 76/30 152 | 68/28 152 |
| 5 MIN. | 80/40 140 | 44/20 144 | 44/20 166 | 64/22 160 | 68/24 164 | 76/32 156 | 70/28 152 |
| 10 MIN. | 80/38 136 | 46/20 148 | 40/20 162 | 66/22 164 | 66/20 160 | 80/32 152 | 70/32 152 |
| 15 MIN. | 76/36 132 | 44/20 148 | 44/20 166 | 62/20 160 | 62/22 164 | 76/30 148 | 74/28 152 |
| 30 MIN. | 76/40 132 | 46/20 144 | 42/20 162 | 60/20 156 | 64/20 160 | 74/20 144 | 68/28 152 |
| 45 MIN. | 78/40 132 | 46/20 148 | 42/20 162 | 62/20 160 | 66/20 160 | 76/30 152 | 68/30 148 |
| 60 MIN. | 78/40 132 | 44/20 144 | 42/20 166 | 62/20 160 | 64/22 160 | 76/28 154 | 68/30 152 |

| PUPIL | 6-1/2M | 7M | 6-1/2M | 7M | 7-1/2M | 7-1/2M | 7M |
| PUPIL E LIGHT | 6-1/2M | 7M | 6-1/2M | 7M | 7-1/2M | 7-1/2M | 7M |

be used as: (1) a decongestive agent; (2) as a value for infiltrative anesthesia; and (3) as a vasoconstrictor in the conjunctival sac. A fourth use is a mydriatic for breaking adhesions, for refraction, for cycloplegia, for overcoming extreme myosis in glaucoma, prior to intraocular surgery, for provocative testing for glaucoma, and as a mydriatic supplement when there is sensitivity to the mydriatic being used.

A drug applied to the conjunctival sac may become absorbed in varying amounts and may have clinically evident systemic reactions not due to hypersensitivity or idiosyncratic reaction. There have been a number of articles written about such events with the ocular use of 10 percent phenylephrine. In 1956,McReynolds et al. used 10 percent phenylephrine ophthalmic solution in 100 hypertensive patients and there were no significant systemic reactions. In six of his cases, there was an elevation of no more than 10 mm Hg. He then reported a case of a subarachnoid hemorrhage
in a 35-year-old man following usage of a
cotton wick soaked with the 10 percent
solution. Previously, one percent atropine
sulfate drops had been used every hour. It
seems possible that the atropine was absorbed
and blocked any vagal stimulus, thus allowing
an exaggerated phenylephrine effect.

In a case described by Lansche in 1966, a
57-year-old diabetic male with rubeosis iridis
developed a blood pressure of 220 mm Hg
following one drop of 10 percent phenylephrine
in an anesthetized eye. His pulse rose to 120.
He turned pale, became faint, began to sweat
profusely and developed a severe occipital
headache without chest pain. Here, the
situation was one of combining a topical anesthetic
with 10 percent phenylephrine in the presence
of conjunctival hyperemia. Apparently, this
allows a greater amount of absorption of the
drug into the blood stream, as if given by
an intravenous injection.

In 1972, Solosko et al reported three cases
of severe hypertension following the use of
ocular solutions. Two of the cases were in their
sixties and in combination with either atropine
or anesthesia. His third case was a three-
month-old female weighing 12 pounds, who
also received atropine both in her conjunctival
sac and intramuscularly. Systemic absorption
of cutaneous and ocular use of atropine is
known to occur. In

In 1973, Borromeo-McGrail et al studied the
effects of 10 percent phenylephrine eye drops
in neonates and reported significant hyper-
tension in low birth-weight infants. In a double-
blind study it was given to three infants, and
in an open trial it was given to eight. The double-
blind revealed a rise of 12-16 mm Hg systolic
and 10-14 mm Hg diastolic pressures. There
was no change in pulse rate. All infants tested
apparently had a “full” pupillary dilatation in
25-30 minutes. Blanching was consistently
observed. Their recommendation of using only
one drop of 2.5 percent phenylephrine is
certainly safe, but impractical for ophthalmology.

In 1949, Heath claimed that he had never
noted or reported damaging effects on ocular
tissues or blood vessels. Sensitivity or delayed
healing have not thus far been reported. However,
there have been several articles written on the direct toxic effects on the eye. In
1961, Mitsui and Takagi, using a five percent
solution in older patients, observed occasional
pigment floaters in the aqueous. These dis-
appeared in 12-24 hours and they were similar
to the melanin of the pigment epithelium of the
iris. Lowenfeld, in a personal communication
with Haddad et al, observed an occasional
rebound miosis in the elderly, and that sub-
sequent use of the drug produced less mydrias-
sis in the elderly than that of the initial
instillation. In a separate study of 32 patients,
Haddad et al reported one case of rebound
miosis in a 50-year-old subject. He also
observed occasional pigmented floaters, prim-
arily in older patients with dark irises. He
described the phenomenon of rebound miosis
as age-related.

Physiologically, when dropped in aqueous
form into the conjunctival sac, a drug enters the
aqueous humor mainly by way of penetration of
the cornea, and in many cases, its effects are
limited to the anterior chamber. Systemic
absorption from the anterior chamber is slow
and limited in degree. If the lens is absent, a
minor amount may distribute posteriorly and if
the quantity is great enough, macular damage
may occur. By placing the drug under a contact
lens or in cotton or using a greater drop
viscosity, prolonged contact with corneal
epithelium is permitted. This allows greater
penetration. This is also true if the cornea is
diseased or damaged. Such is the case also
with local anesthetics, wetting agents, mas-
sage, and abrasions. Theoretically, a compound
must be lipid soluble to penetrate the corneal
epithelium and water soluble to cross the corneal stroma.

Possible mechanisms for rapid systemic
absorption would be via the capillaries within
the conjunctiva. As the drug passes over the
surface of the eye and on through the lacrimal
drainage system, it may be absorbed via the
nasal mucosa. If it reaches the oropharynx or
gastrointestinal tract after swallowing, this
could be another means of absorption. Hyper-
emia of the mucosa and lacrimal duct obstruct-
ion would tend to increase absorption and
conversely, excessive tearing would decrease
absorption. It is worth mentioning that since
the majority of the drug is absorbed prior to
reaching the stomach, it therefore escapes any
metabolic degradation by gastric enzymes.

In January 1974, the British Medical Jour-
na discussed other factors which could explain systemic reactions in our study and in
the previous studies: (1) the dose to body weight
ratio is greater in infants; (2) the mucosa to
which it is accessible is readily permeable to
the drug; and (3) the route of administration bypasses any physiologic transformation of the drug. Furthermore, in a study on preterm infants less than 21 days postnatal life, Nachman et al \(^6\) showed an increased skin permeability by observing degrees of skin blanching from topically applied 10 percent phenylephrine. He observed that infants from 38 to 42 weeks failed to exhibit the response. It was postulated that the barrier function of the epidermis in preterm infants is also immature. It has been shown that absorption of chemicals does occur in nurseries.\(^6\)

**Cyclopentolate: (Cyclogyl)**

Cyclopentolate (B-dimethylaminoethyl-(1-hydroxycyclopentyl)-phenyl acetate hydrochloride)\(^25\) is an anticholinergic mydriatic of basic esters of substituted phenyl acetic acids. It is a white, water-soluble crystalline whose structure follows.\(^25\) to\(^27\)

\[
\text{Cyclopentolate Hydrochloride}
\]

Its effect on the eye is rapid and it has a short duration of action.\(^13\) to\(^28\) In normal subjects, it does not alter intraocular pressure significantly.\(^25\) to\(^29\) However, it may produce acute angle closure glaucoma in susceptible individuals.

This drug has been studied extensively and had previously been devoid of toxic reactions from its ocular usage. Stolzar\(^38\) reported a study of 180 cases without any evidence of general or local toxicity in human subjects and in test animals. Other researchers have shown similar conclusions.\(^25\) to\(^26\)

In 1951, Priestley et al\(^35\) found that when two drops of 0.5 percent cyclopentolate was dropped in each eye five minutes apart, there was "complete" mydriasis of average size 7.0 mm at about one-half hour in Caucasians and at 60 minutes in Negroes.

There have since been several reports of toxic effects with instillation of these eyedrops. In 1962, Simco\(^39\) reported an eight-year-old black female who, following two drops of one percent tropicamide and four drops of one percent cyclopentolate, developed "marked ataxia," dysarthria and incoherent speech along with other evidence of altered cerebellar function. There was no hyperactivity, nor did the patient show changes in temperature, pulse, respiration or become flushed with drug skin and mucous membranes. This incident was duplicated by readministration of six drops of 1 percent solution on a later occasion. He noted also that children with brain damage were even more susceptible to similar reactions. That same year, Beswick\(^40\) reported a case of a nine-year-old white boy, who upon receiving four drops of two percent cyclopentolate, began to hallucinate and actually tried to hide beneath the waiting bench in fear. His reaction lasted about three hours. Following recovery, the child was unable to recall the incident.

In 1963, Mark\(^33\) reported four cases and claimed that side effects to the drug did occur, but infrequently. Reactions consisted of a schizophrenia-like behavior pattern with ataxia. Three of his patients were fourteen years old and younger, and they all had received varying amounts of the one percent solution. Also in 1963, Binkhorst et al\(^37\) conducted a study using two percent cyclopentolate in 40 children and adolescents and a second study of 35 cases using a double-blind approach. He included one percent and two percent cyclopentolate and reported that the two percent solution produced a statistically significant incidence of psychotic reactions characteristic of an acute brain syndrome. There were no significant changes with the one percent solution.

In 1964, Praeger et al\(^41\) reported a case of a seven-year-old white male who, after use of four drops of the two percent solution, manifested signs and symptoms of cerebellar dysfunction and visual hallucinations.

In 1967, Carpenter\(^35\) reported toxicity from four drops of a 0.2 percent solution in an 82-year-old white male who responded by decompensation of a previously compensated chronic dementia. The patient did not return to the "status quo ante," as was the case in all previous reports of toxicity.

In 1970, Adcock\(^36\) reported a four and one-half year-old male Caucasian who received six drops of a two percent solution. The child became markedly flushed and his mucous membranes became dry. This continued over the next hour and was accompanied by periods of wretching, hallucinations, gross ataxia, incoherent babbling, confusion, somnolence, episodes of hyperactivity, an inability to recognize family members, and an acute tachycardia. Central nervous system toxicity lasted about
seven hours, but the tachycardia was noted for 36 hours.

Kenderdell et al reported two cases of grand mal seizures associated with two percent cyclopentolate eyedrops in 1972. One case was an 11-month-old white male who received one drop in each eye. The other was a 12-year-old known epileptic.

In 1973, Bauer et al reported systemic toxicity in newborns. A pair of premature black twins, after eight days of perinatal life, received one drop in each eye of ten percent phenylephrine and one percent cyclopentolate repeated twice at five-minute intervals. Symptoms included vomiting abdominal distention and ileus. After both had apparently recovered, one subsequently died from necrotizing enterocolitis and an intestinal perforation. Intoxication by the drug was confirmed by blood analysis of the infant.

In 1974, a six-year-old girl was reported to have tripped several times on the way home from the office where she had received one percent cyclopentolate and 0.25 percent hyoscine eyedrops. She apparently became very aggressive and said odd things. She was subsequently brought to the accident department actively hallucinating. By the following morning, she had recovered completely without recall of the incident.

Tropicamide: (Mydriacyl)

Tropicamide (N-ethyl-2-phenyl-N-(4-pyridylmethyl)-hydracrylamide) is an anticholinergic mydriatic cycloplegic agent which has become known for its short latency period and its excellent pupillary dilatation. It is very short acting and produces greater mydriasis in subjects with lightly pigmented irises.

Its structure is as follows:

![Tropicamide Structure]

Being an anticholinergic agent, as is cyclopentolate, the mechanism of action in the eye is to block the effects of parasympathetic innervation as well as to block cholinergic drugs acting on the ciliary body and the blood vessels of the eye. In normal eyes, it rarely causes significant alteration of intraocular pressure. However, in open angle glaucomatous eyes, it may cause the pressure to rise. As with cyclopentolate, it may precipitate acute angle closure glaucoma in subjects with shallow anterior chambers and abnormally narrow angles. In animal testing, there have been no detectable histologic abnormalities. Since the drug is not intended for long-term usage, one is not likely to encounter a chronic toxicity. If the drug is absorbed systemically, one would observe classical signs which would include redness and dryness of the skin, dry mouth, increased pulse and body temperature, and disorientation with visual hallucinations.

The only report found in the literature of adverse effects following ocular administration was by Wahl et al. In 1969, he reported an incident, perhaps best described as an acute hypersensitivity to the 0.5 percent solution in a ten-year-old white boy, which read as follows:

Immediately following instillation of one drop of 0.5 percent tropicamide in each eye, he fell from his chair to the floor unconscious.

There was no bowel or bladder incontinence, no psychotic behavior, ataxia, flushing or state of hyperactivity, all of which would be an indication of anticholinergic toxicity.

Simcoe reported that he has used up to ten drops of the one percent solution over a 30-minute period without producing toxic effects.

It is generally agreed that in order to permit adequate examination of the fundus and a thorough examination by slit lamp, a mydriatic agent should produce at least 7 mm dilatation. The most suitable drug would be one which opens the pupil rapidly and painlessly without untoward symptoms. If a problem should occur, as in precipitating acute glaucoma in susceptible individuals, it should be easily counteracted by a mild miotic. In studying the mydriatic effect of 10 percent phenylephrine, Cambill et al measured the responses to a variety of agents by means of an infrared electronic pupillograph. They observed that in adults there is a latency period of approximately 21 minutes with a maximal effect at 65 to 72 minutes. It produced less dilatation than tropicamide. It has also been demonstrated that dilatation varies with eye color. The least dilatation was observed in hazel-eyed subjects and the greatest was noted in those with blue irises. It was further demonstrated that there was almost identical mydriasis produced with both 10 percent and 2.5 percent phenylephrine solutions.
CONCLUSION

Many drugs used as drops are absorbed systemically and cause changes in vital signs. We have shown this to be the case with several of the more common mydriatics. If an agent has the potential to cause an elevation in blood pressure, it may well do so after ocular instillation. In a newborn especially if preterm, such an occurrence could precipitate or further a cerebral hemorrhage. It would seem imperative that blood pressures be known prior to the use of such agents and if they are elevated, then use should be avoided.

Ten percent aqueous and viscous phenylephrine causes blanching of the skin around the eyes of newborns. In most cases, it raises both systolic and diastolic blood pressures.

Ten percent aqueous or viscous phenylephrine, one percent cyclopentolate, one percent tropicamide and 2.5 percent phenylephrine, when used alone in our study for a total dosage of three drops in each eye, did not provide adequate dilatation to view the periphery or the retina. This is essential for identifying the early changes seen in retrolental fibroplasia.

Our "combination drop" protocol is effective in providing an average dilatation equal to or greater than 7.0 mm in the presence of a high intensity spotlight. Using separate dropper bottles and placing a total of three drops in each eye, we observed average dilatation of 7.7 mm. In two cases of this series, there was an elevation of blood pressures with no variation of heart rate. Cyclopentolate may cause an elevation of heart rate when used as a one percent solution for eyedrops.

In an attempt to facilitate the application of drops and to lessen the concentrate of cyclopentolate, we prepared a 15 cc dropper solution containing 2.5 percent phenylephrine, one-half percent cyclopentolate and one-half percent tropicamide. With one drop in each eye repeated twice at five minute intervals for a total of six drops we observed average dilatation of 7.1 mm without any skin blanching or changes in pressures or heart rates. With a second group of seven babies we then applied only one drop in each eye. There were no changes in pressures or heart rates. After one hour the average dilatation was 7.0 mm.

It is obvious from this study that the use of 2.5 percent phenylephrine alone is not adequate for proper examination of the retina with the indirect ophthalmoscope. The original protocol of nine drops, although safe by our testing, certainly may have toxic effects. Therefore, the single instillation of our combination drops proved to be very effective while safe and we recommend it highly in examination of newborns in the nursery.

SUMMARY

During routine dilatation of 48 newborns, systemic responses and pupil dilatation were monitored. Both 10 percent aqueous and viscous phenylephrine caused blanching around the eyes and produced considerable rise in blood pressure. Dilatation average 4.7 mm. In a double blind study, a 2.5 percent solution caused no skin blanching and no change in pressure or heart rate. Average dilatation was 4.5 mm.

No blood pressure changes were observed with either one percent cyclopentolate or one percent tropicamide. Average dilatations were 5.0 mm and 5.3 mm respectively.

The above agents, used individually for a total dosage of three drops in each eye did not provide adequate dilatation for a thorough funduscopic examination.

Our protocol at United Hospitals Medical Center is a safe combination of drugs and provides excellent dilatation averaging greater than 7 mm. No skin blanching or change in heart rate was observed.

REFERENCES