No More 'Squint' Please

To the Editor:

Not to take anything away from this fine investigative work,[1] we would plead with the authors (and this journal and ARVO) not to use the term "squint."

There are a number of reasons for making this request:

The authors are, of course, talking about the medical entity termed strabismus, which historically has been called squint. However, the general population does not recognize this use of the word squint. As defined by the American Heritage Dictionary, squint means to look with the eyes partly open; to look or glance to the side; to suffer from strabismus; and to have an indirect or implicit tendency.

1. Note that the primary use is as a verb, not as a noun.
2. Strabismus is only the third meaning and it is not a synonym, even there, because strabismus is a noun.
3. Lay people think of squinting first and second as narrowing of the palpebral fissures, usually associated with attempts to see more clearly, especially as in myopia. This is obviously a very different condition from the binocular misalignment, properly called strabismus. To avoid the high probability of creating confusion with our patients and the general public, we strongly advocate and request that the term squint not be used when referring to strabismus.
4. Nor is the word squint a neutral scientific term. Rather, "Superstition and folklore that label a squinter as being shifty-eyed, evil-eyed, and not to be trusted and apt to lie are still strong in our allegedly enlightened world . . . The German word for squinting is schielen. To look at something mit schielenden Augen is equivalent to 'envy' or to 'begrudge.' The French word for squint is loucher; and to this day a shady business deal is referred to in French as une affaire louche."[2]
5. You will find most of the English-speaking medical profession has essentially abandoned the term squint in preference to strabismus for the foregoing reasons. Books and journals about strabismus may include the term strabismus in the title and text, but the term squint is rarely, if ever, used there.
6. As a specific example, as editorial policy, we absolutely prohibit, from the pages of our journal Binocular Vision & Strabismus, the use of the term squint for all of the foregoing reasons.

We would also note that the authors seem to have themselves coined the new acronym and term ISS (infantile squint syndrome) in that they offer no reference for the term in the introduction of this article. We would greatly appreciate it if they would uncoin this ISS. We do realize that they have defined their syndrome as present in children specifically younger than 1 year of age and that this, is therefore, not precisely equitable with similar terms such as neonatal, infantile strabismus, or infantile esotropia. There is, to my knowledge, no medical or scientific term that means "1 year of age." But it is not so important to have a new term as it is to simply define, as they have, the ages of the group or groups they are investigating. This they have done. They don't have to create a new disease!

Congratulations to the authors once again for an otherwise fine piece of work.

Paul E. Romano, Editor
Binocular Vision & Strabismus

References

1. Schor CM, Fusaro RE, Wilson N, McKee SP. Prediction of early-onset esotropia from components of the infantile squint syndrome. *Invest Ophthalmol Vis Sci.* 1997;38:719–740.
2. von Noorden GK. *Binocular Vision and Ocular Motility. Theory and Management of Strabismus.* 5th ed. St Louis: Mosby–Year Book; 1996:153.

The authors reply:

Though Dr. Romano may be correct in suggesting that the term "squint" is ambiguous to a lay audience, the term is used frequently as an abbreviation by the vision health professionals who are more likely to read our article. The term squint has been in widespread use since the turn of the century.[1–8] We would not argue with the definition in the *American Heritage Dictionary* but would prefer to use the definition cited in medical dictionaries such as Stedman's or Dorland's, both of which define squint exclusively as strabismus.[9,10] Romano finds the term squint objectionable, and we are willing use the term infantile strabismus syndrome (ISS).

Romano questions whether the term ISS can be

equated with such terms as neonatal or infantile strabismus or infantile esotropia. The term ISS is not meant to be equated with these forms of strabismus. It is a collection of symptoms that have been observed clinically to be associated with infantile strabismus.

It is important to distinguish between the primary condition infantile strabismus and an associated syndrome. A syndrome is defined in *Webster's New World Dictionary* as a number of symptoms occurring together and characterizing a specific disease or condition or a set of characteristics regarded as identifying a certain type of condition. Stedman's and Dorland's medical dictionaries define syndrome as a set of symptoms that occur together; the sum of signs of any morbid state; a symptom complex. In the case of ISS, the condition is infantile strabismus and the syndrome is composed of DVD, latent nystagmus, and directional asymmetries of monocular OKN, pursuits and motion perception. Our article[11] investigates whether this group of anomalies constitutes a syndrome associated with infantile strabismus by describing how the presence of some or all of these symptoms can be used retrospectively to estimate the probability that strabismus observed in an adult patient had an age of onset within the first year of life.

The probability of infantile strabismus is greater in an adult strabismic amblyopic patient who exhibits more than one of the syndrome components, such as asymmetric monocular smooth pursuit and DVD (see Tables 6 and 7 on page 730 and the Discussion on page 733 of our article).[11] This suggests there is some value in considering these directional disturbances collectively as a syndrome rather than individually.

Finally, the ISS is not a new disease entity. Again, we consider infantile strabismus to be the primary disease. We cite many prior studies that consider several of these conditions collectively as associated with infantile strabismus, and we have consolidated these conditions in terms of a syndrome that, for example, may be used to estimate the period of strabismus onset. There also have been attempts to predict infantile strabismus retrospectively from the presence of its associated motor anomalies.[12–15] An overview of the components that make up the ISS can be found in Adler's Physiology of the Eye: Clinical Applications.[16] These resources, as well as others, consider DVD and latent nystagmus together, sometimes in association with asymmetries of pursuits, or OKN or motion perception as a predictor of infantile strabismus. Ours is the first article that has considered all these abnormalities en masse in a large population-based study. The results indicate that among adult strabismic amblyopes, DVD and asymmetries of pursuits and OKN, have the highest predictive value for infantile strabismus when considered in context with the baseline prevalence of infantile strabismus in the population from which the sample has been drawn.

Clifton M. Schor
Robert E. Fusaro
Nance Wilson
Suzanne P. McKee

References

1. Worth CA. *Squint: Its Causes, Pathology and Treatment.* Philadelphia: P. Blakiston's Son & Co; 1906.
2. Chavasse F. *Worth's Squint or the Binocular Reflexes and the Treatment of Strabismus.* 7th ed. London: Bailliere Tindall and Cox; 1939.
3. Lyle TK, Bridgeman GJO. *Worth and Chavasse's Squint: The Binocular Reflexes and the Treatment of Strabismus.* 8th ed. Philadelphia: Blakiston; 1950.
4. Lyle TK. *Lyle and Jackson's Practical Orthoptics in the Treatment of Squint and Other Anomalies.* 5th ed. London: Lewis & Co; 1967.
5. Duke E. *System of Ophthalmology, vol VI: Ocular Motility and Strabismus.* London: Henry Kimpton; 1973.
6. Krimsky E. *The Management of Binocular Imbalance.* Philadelphia: Lea & Febiger; 1948.
7. Maddox EE. *Tests and Studies of the Ocular Muscles.* Philadelphia: Keystone Publishing; 1907.
8. Keiner GBJ. *New Viewpoints on the Origin of Squint.* The Netherlands: The Hague; 1951.
9. Dorland's Illustrated Medical Dictionary. 28 ed. Philadelphia: WB Saunders; 1994.
10. Stedman's Medical Dictionary. 25th ed. Baltimore: Williams & Wilkins; 1990.
11. Schor CM, Fusaro RE, Wilson N, McKee SP. Prediction of early-onset esotropia from components of the infantile squint syndrome. *Invest Ophthalmol Vis Sci.* 1997;38:719–740.
12. Bourron–Madignier M, Ardoin ML, Cypres C, Vettard S. Study of optokinetic nystagmus in children. In: Lenk–Schafer M, ed. *Transactions of the Sixth International Orthoptic Congress.* Harrogate, UK: International Orthoptic Congress; 1987:134–139.
13. Demer JL, von Noorden GK. Optokinetic asymmetry in esotropia. *J Ped Ophthalmol & Strabismus.* 1988;25:286–292.
14. Mein J. The OKN response and binocular vision in early onset strabismus. *Aust Orthoptic J.* 1983;20:13–17.
15. Kommerell G. Ocular motor phenomena in infantile strabismus. In: Lennerstrand G, vonNoorden GK, Campos EC eds. *Strabismus and Amblyopia.* London: Macmillan Press. 1988:99–109.
16. Tyschen L. Binocular vision. *Adler's Physiology of the Eye: Clinical Applications.* 9th ed. St. Louis: Mosby; 1992:773–854.

Hyperglycemic Cytosolic Reductive Stress 'Pseudohypoxia': Implications for Diabetic Retinopathy

To the Editor:

The objective of a recent article by Winkler et al[1] was to test the hypothesis of Van den Enden et al[2] that elevated glucose levels induce a "hypoxia-like" metabolic imbalance (pseudohypoxia) that may contribute to diabetic retinopathy. Van den Enden et al reported that aerobic incubation of retinas from normal rats at elevated glucose levels induced a cytosolic redox imbalance like that observed in retinas of diabetic rats, i.e., an increased lactate/pyruvate ratio indicative of an increased cytosolic ratio of free NADH/NAD^+ (because of the near-equilibrium between the two ratios established by lactate dehydrogenase[1]). They also reported that increased retinal lactate/pyruvate ratios and triose phosphates at elevated glucose levels, as well as increased retinal sorbitol levels and fructose production, were prevented by an inhibitor of the sorbitol pathway. Surprisingly, Winkler et al did not measure retinal lactate/pyruvate ratios, the increase in which is the cornerstone of the Van den Enden hypothesis. Nor did Winkler et al measure triose phosphates, sorbitol, fructose, or the effects of a sorbitol pathway inhibitor; yet, they concluded that their experiments and calculations enabled them to test critically and refute the hypothesis of Van den Enden et al.

We disagree with the conclusions of Winkler et al, and we take issue with their position that studies designed to evaluate potential mechanisms of diabetic retinopathy should focus on retinal capillary cells (to the exclusion of neural and glial cells), i.e., that measurement of whole retinal lactate and pyruvate content is meaningless. In view of the potentially important role of vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy, it is noteworthy that elevated glucose levels (independent of hypoxia) increase VEGF mRNA and protein levels in retinal pigment epithelial cells[3] and that VEGF immunoreactivity is increased in retinal glial cells remote from sites of nonperfusion (hypoxia) and angiogenesis in retinas of persons with diabetes.[4]

The comment that the validity of the Van den Enden et al hypothesis requires that oxidation of sorbitol to fructose must account quantitatively for the increase in retinal lactate is inconsistent with the relationship between the NADH/NAD^+ and lactate/pyruvate ratios and evidence that the lactate/pyruvate ratio can be increased despite a decrease in lactate level depending on the experimental conditions (ref. 47 in Van den Enden et al). It is the increase in lactate/pyruvate ratio, not in retinal lactate content per se, that reflects the increased cytosolic-free NADH/NAD^+ resulting from increased oxidation of sorbitol to fructose. Because of the low ratio of cytosolic-free NADH/NAD^+ ($\sim 2.7 \times 10^{-3}$) at normal glucose levels, even a small increase in the rate of oxidation of sorbitol to fructose and associated accumulation of NADH can markedly increase NADH/NAD^+ and lactate/pyruvate ratios (possibly because of the limited capacity of glycerol phosphate and malate aspartate shuttles to transport reducing equivalents from the cytosol to the mitochondria).

Winkler et al concluded that retinal lactate and ATP levels, as well as lactate production by retinas incubated in 5 mM glucose, was limited by the rate of glucose diffusion from the incubation medium into the retina. This conclusion is inconsistent with their finding that lactate production by retinas in 5 mM glucose was doubled by inhibition of oxidative metabolism (Table 1). The data in Table 3 are consistent with the concept of pseudohypoxia and with observations of Nyengaard et al[5] that hypoxia and elevated glucose levels increase the retinal lactate/pyruvate ratio by different mechanisms. The high lactate levels in freshly isolated normal retinas may reflect hypoxia or pseudohypoxia because these retinas were from rats sedated by carbon dioxide narcosis, which acutely increases blood flow (consistent with hypoxia/pseudohypoxia) and alters energy metabolism by mechanisms that are not understood.

Winkler et al suggest that aerobic lactate production in the study by Van den Enden et al is approximately two times higher than that reported by other investigators. This conclusion was based on an estimated value of 250 μg DNA/retina, which is probably erroneous in view of methodological limitations noted by Noell et al.[6] Using 10 mg wet weight per retina assumed by Winkler et al, the DNA content of rat retinas is only 97 μg[7] to 117 μg (unpublished data from our laboratory). Lactate production based on our DNA values is 1.52 μmol/hour per retina in 5 mM glucose in the experiments of Van den Enden et al, which is identical to that reported by Winkler et al.

In our view, the experiments and calculations reported by Winkler et al did not test the hyperglycemic pseudohypoxia hypothesis and do not support their conclusions that glucose diffusion (at 5 mM glucose) was rate limiting for lactate production or that lactate production was anomalous in the experiments of Van den Enden.

Yasuo Ido
Joseph R. Williamson
Washington University School of Medicine
St. Louis, Missouri

References

1. Winkler BS, Arnold MJ, Brassell MA, Sliter DR. Glucose dependence of glycolysis, hexose monophosphate shunt activity, energy status, and the polyol pathway in retinas isolated from normal (nondiabetic) rats. *Invest Ophthalmol Vis Sci.* 1997;38:62–71.
2. Van den Enden MK, Nyengaard JR, Ostrow E, Burgan JH, Williamson JR. Elevated glucose levels increase retinal glycolysis and sorbitol pathway metabolism: Implications for diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1995;36:1675–1685.
3. Sone S, Kawakami Y, Okuda Y, et al. Vascular endothelial growth factor is induced by long-term high glucose concentration and up-regulated by acute glucose deprivation in cultured bovine retinal pigmented epithelial cells. *Biochem Biophys Res Commun.* 1996;221:193–198.
4. Amin RH, Frank RN, Kennedy A, Eliott D, Puklin JE, Abrams GW. Vascular endothelial growth factor is present in glial cells of the retina and optic nerve of human subjects with nonproliferative diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1997;38:36–47.
5. Nyengaard JR, Ostrow E, Burgan JR, Smith, SR, Williamson JR. Interactions between hyperglycemia- and hypoxia-induced redox changes in rat retinas. ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1994;35:1734.
6. Noell WK, Organisciak DT, Ando H, Braniecki MA, Durlin C. Ascorbate and dietary protective mechanisms in retinal light damage of rats: Electrophysiological, histological and DNA measurements. In: Hollyfield JF, Anderson RE, La Vail MM, eds. *Degenerative Retinal Disorders: Clinical and Laboratory Investigations.* New York: Alan R. Liss; 1987:469–483.
7. Dewar AJ, Barron G, Yates CM. The effect of light deprivation on the progress of retinal degeneration in two strains of dystrophic rat. *Exp Eye Res.* 1975;21:507–514.

The authors reply:

We first encountered hyperglycemic pseudohypoxia in an article published in 1993 in the journal *Diabetes* by Williamson et al.[1] These authors proposed that hyperglycemia stimulates the rate of the NAD-dependent oxidation of sorbitol to fructose, which causes an increase in the cytosolic ratio of NADH-to-NAD as measured by an increase in the ratio of lactate-to-pyruvate. Williamson et al[1] suggested that this redox imbalance causes tissue dysfunction in diabetes. Because hypoxia causes a similar redox imbalance, i.e., increases in NADH-to-NAD and lactate-to-pyruvate ratios, as does hyperglycemia, Williamson coined the combined terminology. We were intrigued with this hypothesis and its implications, in part because Williamson et al indicated in their article (page 802) that the retina manifested hyperglycemic pseudohypoxia, though no data on the retina were presented. Subsequently, Van den Enden et al[2] published data on the rat retina that supported the hyperglycemic pseudohypoxia hypothesis. We were impressed with this article initially, but subsequent readings revealed the absence of quantitative arguments. We therefore sought to test their hypothesis (we are the first to do so) in a quantitatively rigorous way.[3] We feel we succeeded, but Ido and Williamson do not. So, let's proceed to the issues, starting with the easy ones and progressing to the cornerstone of their argument.

The value we used for DNA content/retina, 250 μg, was based on published data for visual cell DNA (175 μg) obtained using a dye-binding fluorescence technique.[4] We assumed that visual cell DNA accounts for 75% of total retinal DNA and came up with 250 μg. Katz and Robison,[5] though not referenced in our article, reported the DNA content of a rat retina was 260 μg (page 301), as measured by thymine concentrations in formic acid digests using HPLC. Further, Noell et al[6] only cautioned (page 470) that "the DNA test requires that for every sample exactly the whole retina is peeled off the eye with the ciliary rim attached"; this can hardly be considered a "methodological limitation." Van den Enden et al did not report values for DNA content/retina, though virtually all their data were presented on a per μg DNA basis, so it is most surprising to see 2 years later a value that is presented as "unpublished data from our laboratory." Even if we adopt the lower DNA value so that their glycolytic rate matches ours, this does not change our view about their hypothesis because the levels of metabolites, e.g., sorbitol, lactate, pyruvate, and so on, calculated on a per retina basis all decrease proportionately.

Several reports in the literature[7–9] indicate that for the isolated rat retina, the ratio of NADH-to-NAD is in the range between 1-to-3 and 1-to-7, which is 50- to 100-fold greater than the (uncited) ratio stated by Ido and Williamson, i.e., 2.7×10^{-3} or 1-to-370. It surprises us that Ido and Williamson raise a concern about our suggestion that studies on mechanisms of diabetic retinopathy ought to focus on retinal capillary cells. We agree that it is unwise to neglect the glia and RPE cells (isolated retinas, however, lack the RPE) in such studies. However, we did not state that "measurement of whole retinal lactate and pyruvate content is meaningless." Rather, we simply put forward a caution (page 70) about extrapolating whole retinal measurements of lactate and pyruvate to a particular cell type, especially when that cell type (endothelial cells and Müller cells, for example) makes up a small fraction of the tissue.

Now to the central question: Did our experiments[3] test the hyperglycemic pseudohypoxic hypothesis? The cornerstone of this hypothesis is that the

ratio of lactate-to-pyruvate is increased in response to activation of the sorbitol pathway by elevated glucose. But, as reported by Van den Enden et al[2] (page 1678), "increased retinal lactate-pyruvate ratios in 30 versus 5 mM glucose were accounted for by an approximately twofold increase in lactate content versus only an approximately 30% increase in pyruvate." Because Van den Enden et al do not provide values for the retinal content of lactate and pyruvate in fresh (see later) or incubated tissues, we calculated these values, respectively, from their statements on page 1678: "retinal lactate accounted for 1.5% of total lactate production" and "retinal pyruvate accounted for 0.8% of total pyruvate production." Using data from Van den Enden et al for 5 mM glucose, retinal lactate is 97.5 nmol/retina (26 nmol/μg DNA $\times$ 250 μg DNA/retina $\times$ 0.015) and retinal pyruvate is 4.3 nmol/retina (2.13 nmol/μg DNA $\times$ 250 μg DNA/retina $\times$ 0.008), whereas in 30 mM they reported that retinal lactate increased twofold (to 195 nmol/retina) and pyruvate increased by 30% (to 5.5 nmol), and the lactate-to-pyruvate ratio increased 1.6-fold. The hyperglycemic-induced increase in retinal lactate is 97.5 nmol (48.75 glucose equivalents), but the increase in pyruvate is only 1.2 nmol. This shows that the increase in retinal lactate content (in nmoles) accounts for virtually all of the 1.6-fold increase in the ratio of lactate-to-pyruvate found by Van den Enden in the presence of 30 mM glucose. This is the reason we feel that measurements of lactate content alone provided us[3] with enough quantitative information to test their hypothesis. Had Van den Enden et al found that the hyperglycemic-induced 1.6-fold increase in the lactate-to-pyruvate ratio was caused by a decrease in pyruvate content, then testing their hypothesis would have been difficult, if not impossible, because the maximum decrease in pyruvate would be less than 2 nmol, e.g., from 4.3 to 2.7 nmol/retina. The reference cited by Ido and Williamson (reference in Van den Enden et al) for an increase in the ratio of lactate-to-pyruvate when both lactate and pyruvate decrease (page 517) relates to the specific case of a starved animal.[10]

Using data from Van den Enden et al, we[3] calculated that the flux of glucose through the polyol pathway in hyperglycemia (as estimated from their values for sorbitol content and fructose production) could account for only 15% of the increase in lactate content, i.e., the lactate-to-pyruvate ratio, a result clearly at odds with their hypothesis. Quite frankly, this calculation was unexpected, and so we set out to test the hyperglycemic pseudohypoxia hypothesis by measuring the glucose-dependence of glycolysis, activity of aldose reductase, retinal content of polyols and lactate, and the hexose monophosphate shunt in isolated rat retinas, the latter measurement (surprisingly not mentioned by Ido and Williamson) providing a direct quantitative estimate of the NADPH-dependent flux of glucose through the polyol pathway which could be compared to changes in retinal lactate content. Our results and quantitative calculations (please see our article[3]) do not support the hypotheses of Williamson et al and Van den Enden et al because the magnitude of the glucose-dependent increase in retinal lactate content is 6 to 7-fold greater than the maximum possible flux through the polyol pathway.

This leaves us with explaining why we think that diffusion of glucose into the retina may be limited somewhat when the incubation medium contains 5 mM glucose. A simple answer is that the rates of aerobic and anaerobic glycolysis and aerobic and anaerobic retinal adenosine triphosphate content are higher when the retinas are bathed in 10 mM glucose. Indeed, these effects are similar to findings showing that the rate of respiration in the isolated rat retina is increased when the partial pressure of oxygen in the incubation medium is increased from 20% (ambient) to 50% to 95%.[11] Undoubtedly, effects of unstirred boundary layers and other unknown factors influence the nature of these findings. We should point out that inhibition of oxidative metabolism leads to an increase in the rate of glycolysis (Pasteur effect) in isolated rat retinas even when the incubation medium contains 1 mM glucose,[12] a condition in which the availability of substrate is clearly not optimal. Our view is that on switching from aerobic to anaerobic conditions, the increase in the rate of lactic acid production results in a steeper transmembrane glucose gradient, i.e., the intracellular concentration of glucose is decreased, thereby enabling glucose to enter retinal cells at faster rates over a wide range of extracellular glucose concentrations. And finally, Ido and Williamson suggest that the level of lactate in our fresh retinas is high because of hypoxia related to carbon dioxide-induced narcosis. This is clearly a generic concern for all such in vitro measurements. Because our fresh values for adenosine triphosphate are very close to the values obtained in our aerobic incubations, we do not feel that our fresh lactate values reflect hypoxia.

We realize that the hyperglycemic pseudohypoxia hypothesis is seemingly entrenched in both the diabetes and the ocular literature.[13,14] However, we believe that our conclusions, drawn from quantitative studies using whole rat retinas, are justified and that the hyperglycemic pseudohypoxia hypothesis should be reconsidered.

Barry S. Winkler
Matthew J. Arnold
Melissa A. Brassell
Denise R. Sliter
Oakland University
Rochester, Michigan

References

1. Williamson JR, Chang K, Frangos M, et al. Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes.* 1993;42:801–813.
2. Van den Enden K, Nyengaard JR, Ostrow E, Burgan JH, Williamson JR. Elevated glucose levels increase retinal glycolysis and sorbitol pathway metabolism. *Invest Ophthalmol Vis Sci.* 1995;36:1675–1685.
3. Winkler BS, Arnold MJ, Brassell MA, Sliter DR. Glucose dependence of glycolysis, hexose monophosphate shunt activity, energy status, and the polyol pathway in retinas isolated from normal (nondiabetic) rats. *Invest Ophthalmol Vis Sci.* 1997;38:62–71.
4. Organisciak DT, Wang H-M, Xie A, Reeves DS, Donoso LA. Intense-light mediated changes in rat rod outer segment lipids and proteins. In: LaVail MM, Anderson RE, Hollyfield JE, eds. *Inherited and Environmentally Induced Retinal Degenerations.* New York: Alan R. Liss; 1989:493–512.
5. Katz ML, Robison W Jr. Evidence of cell loss from the rat retina during senescence. *Exp Eye Res.* 1986;42:293–304.
6. Noell WK, Organisciak DT, Ando H, Braniecki MA, Durlin C. Ascorbate and dietary protective mechanisms in retinal light damage of rats: electrophysiological, histological and DNA measurements. In: Hollyfield JE, Anderson RE, LaVail MM, eds. *Degenerative Retinal Disorders: Clinical Laboratory Investigations.* New York: Alan R. Liss; 1987:469–483.
7. Heath H, Rutter AC, Beck TC. Reduced and oxidized pyridine nucleotides in the retinae from alloxan-diabetic rats. *Vision Res.* 1962;2:333–342.
8. Graymore CN, Towlson MJ. The metabolism of the retina of the normal and alloxan diabetic rat. *Vision Res.* 1965;5:379–389.
9. Giblin FJ, Reddy VN. Pyridine nucleotides in ocular tissues as determined by the cycling assay. *Exp Eye Res.* 1980;31:601–609.
10. Williamson DH, Lund P, Krebs HA. The redox state of free nicotinamide-adenine dinucleotide in the cytoplasm and mitochondria of rat liver. *Biochem J.* 1967;103:514–527.
11. Winkler BS. A quantitative assessment of glucose metabolism in the isolated rat retina. In: Christien Y, Doly M, Droy–LeFaix MT, eds. *Les Seminaires Ophthalmologiques d'IPSEN. Tome 6. Vision and Adaptation.* Paris: Elsevier; 1995:78–96.
12. Winkler BS. Glycolytic and oxidative metabolism in relation to retinal function. *J Gen Physiol.* 1981;77:667–692.
13. Amin RH, Frank RN, Kennedy A, Eliott D, Puklin JE, Abrams GW. Vascular endothelial growth factor is present in glial cells of the retina and optic nerve of human subjects with nonproliferative diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1997;38:36–47.
14. Gillies MC, Su T, Stayt J, Simpson JM, Naidoo D, Salonikas C. Effect of high glucose on permeability of retinal capillary endothelium in vitro. *Invest Ophthalmol Vis Sci.* 1997;38:635–642.