Albrecht von Graefes Arch Klin Ophthalmol
(1981) 215:193–201

Graefes Archiv
für klinische und experimentelle
Ophthalmologie

Etomidate Induced Retinal Changes

Magdolna Antal*
Postgraduate Medical School, Clinic of Urology, H-1135 Budapest, Szabolcs u. 35, Hungary

Abstract. The author examined the effect of etomidate-anaesthesia of one hour duration on the ultrastructure of the retina in animal experiments. Immediately after the exposure only the Müller's cells were moderately damaged. One day following the narcosis more serious pathological changes developed in the external nuclear layer which were partly irreversible. The changes found in the internal nuclear layer were less serious. The structure of the glial cells also altered. In the specimens taken 48 h following the anaesthesia the pathological changes of the neurons regressed to some degree, the Müller's cells reorganised and masses of glycogen accumulated in them. Further studies are needed to explain the eventual retinal toxic effect of this agent.

Zusammenfassung. Die vorliegende Arbeit untersucht den Einfluß einer Etomidate (Hypnomidate®)-Anästhesie auf die Ultrastruktur der Retina im Tierexperiment.

Unmittelbar nach der Exposition gegenüber Etomidate lassen sich nur mäßige Schädigungen in den Müllerschen Zellen nachweisen. Einen Tag nach der Narkose finden sich deutlich ausgeprägtere pathologische Veränderungen in der äußeren nukleären Schicht, die teilweise irreversibel waren. Die in der inneren nukleären Schicht gefundenen Veränderungen waren weniger ausgeprägt. Zusätzlich fanden sich auch Veränderungen in der Gliazellstruktur. In den Gewebsproben, die 48 Std nach der Narkose präpariert wurden, waren die Veränderungen in den Neuronen teilweise wieder zurückgebildet und die Müllerschen Zellen reorganisiert mit deutlichen Ansammlungen von Glykogen-Granula in den Müllerschen Zellen. Weitere Studien sind notwendig, um den möglichen toxischen Effekt von Etomidate auf die Retina zu untersuchen.

Introduction

Hypoxic cortical damage may be the cause of the side effects of some drugs including some anaesthetic agents. In previous studies characteristic retinal

* *Present Address:* Department of Anaesthesiology and Intensiv Care of "Jahn Ferenc" Hospital, H-1204 Budapest, Köves ut 2–4, Hungary

0065-6100/81/0215/0193/$01.80

changes brought about by hypoxia as well as by ketamine anaesthesia were found [2, 11, 12]. Following the studies of ketamine and Althesin anaesthesia, this paper deals with the retinal effect of another barbiturate-free agent – etomidate.

Materials and Methods

Pigmented rabbits of 1,500–3,000 g body weight were used for the experiments. Narcosis was induced without premedication by injecting 2 mg/kg body weight of etomidate (Hypnomidate, Janssen) into the marginal ear vein.

The narcosis was maintained 1 h with repeated doses. In the first group of animals one of the eyes was removed by 5 min of anaesthesia; these eyes served as controls. The other eye was removed after 60 min of anaesthesia. In the other group, one eye was removed after anaesthesia of 60 min duration, and the other eye 20–48 h following anaesthesia, respectively.

Specimens of the central and peripheral parts of the retinas were taken for examination (1-mm^3 pieces) and fixed in 2% osmium tetroxide. After dehydration the material was embedded in araldite, contrasted in uranyl acetate, and sectioned on a Reichert's ultramicrotome. The sections were examined and photographed by a JEM 7A electron microscope.

Results

The structure of the control eyes enucleated by 5 min of anaesthesia was intact and corresponded to the well-known appearance of the normal rabbit retina. The Müller's cells contained glycogen, a phenomenon common during natural sleep (Fig. 1).

The neurons of the retinas removed after 60 min of anaesthesia were not remarkably damaged. The photoreceptors, bipolar, and ganglion cells equally exhibited a normal structure. The synapses showed no alterations in either the external or internal plexiform layers. The glycogen seen in the control retinas disappeared, however; the structure of the smooth surfaced endoplasmic reticulum became loosened, and the density of the vesicles decreased. Some larger vacuoles could be identified in some places (Figs. 2 and 3).

By h 20 following anaesthesia, the neurons of the retina exhibited noticeable pathological changes. The outer and inner segments of the photoreceptors seemed to remain intact but perinuclear cisterns developed around their nuclei. In the external nuclear layer pyknotic nuclei were often observed. Perinuclear cisterns also occurred around the nuclei of the bipolar, horizontal, and Müller's cells. In the inner layers these changes could not be observed. The structure of the ganglion cells seemed to be normal, and the inner plexiform and nerve fibre layers were also intact. Glycogen was not seen in the Müller's cells and instead of the normal vesicular system of the endoplasmic reticulum, masses-appeared made up partly of huge vacuoles and partly of filaments.

By the h 48 following anaesthesia, the smaller or bigger perinuclear cisterns around the nuclei of the photoreceptors had not yet disappeared. The amount of pyknotic nuclei was similar to that seen at the 20 h interval following anaesthesia. The changes in the inner nuclear layers had almost regressed, small perinuclear cisterns being only occasionally apparent. The ganglion cells and the plexiform layers were intact. In most of the Müller's cells the usual system of endoplasmic reticulum became reorganised, although in some places the vacuoles and in

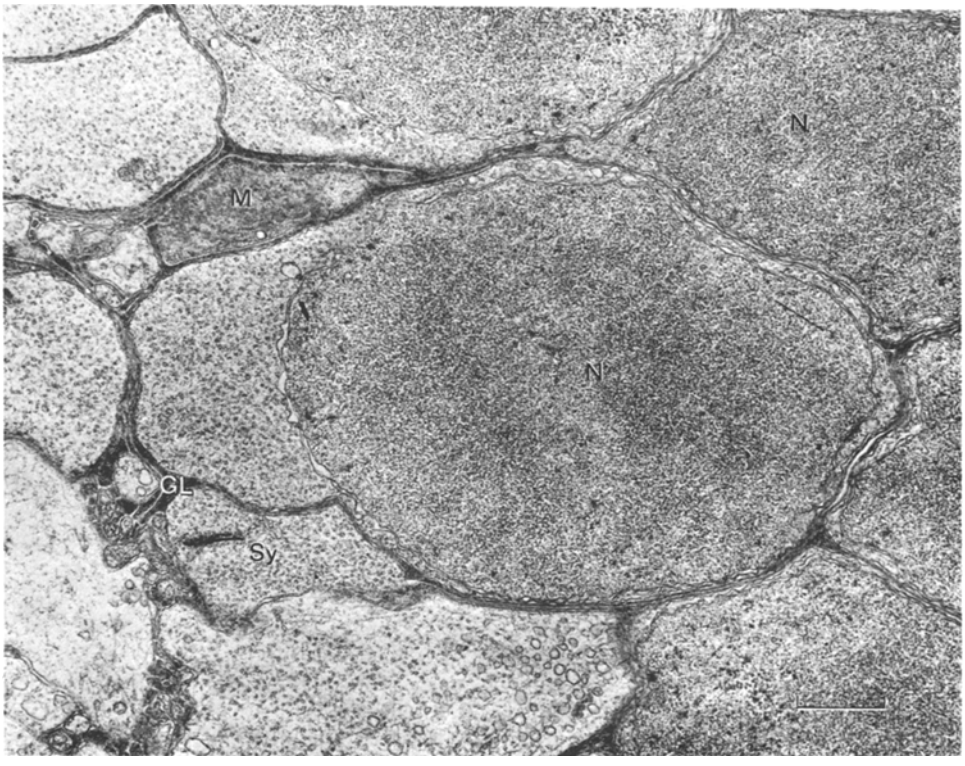

Fig. 1. Area of the retina at the border of the inner nuclear and inner plexiform layer at min 5 of anaesthesia. × 19,200. *N* nucleus of the photoreceptor; *Sy* synapsis; *M* Müller's cell process; *Gl* Glycogen

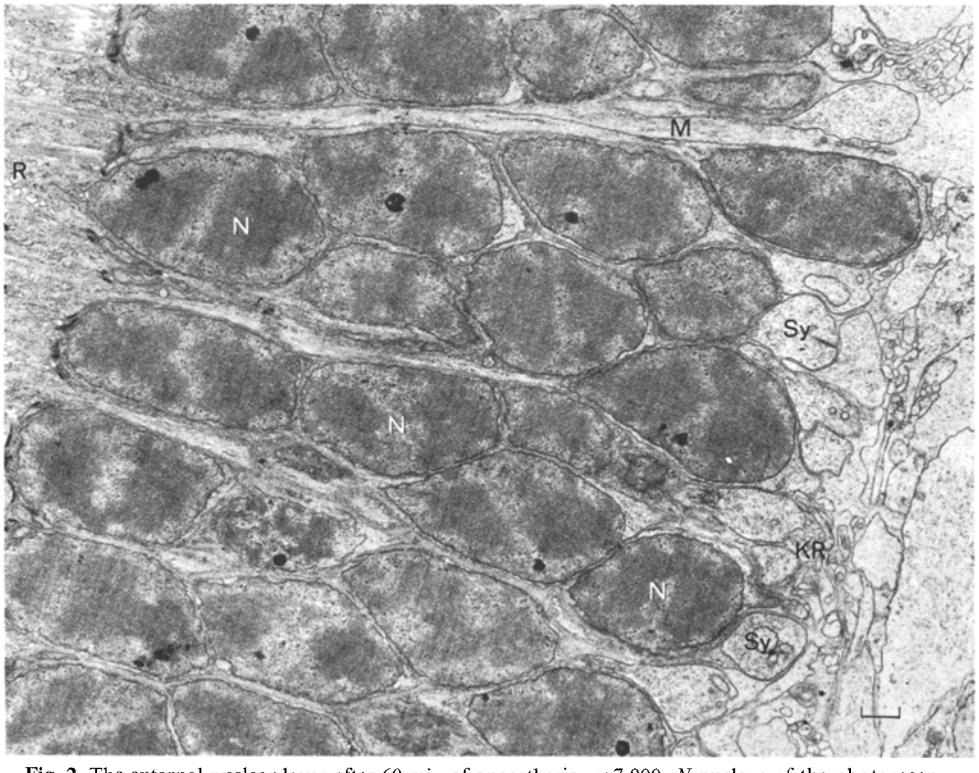

Fig. 2. The external nuclear layer after 60 min of anaesthesia. × 7,000. *N* nucleus of the photoreceptor; *KR* external plexiform layer; *Sy* Synapsis; *R* inner segment of the photoreceptor's process; *M* Müller's cell

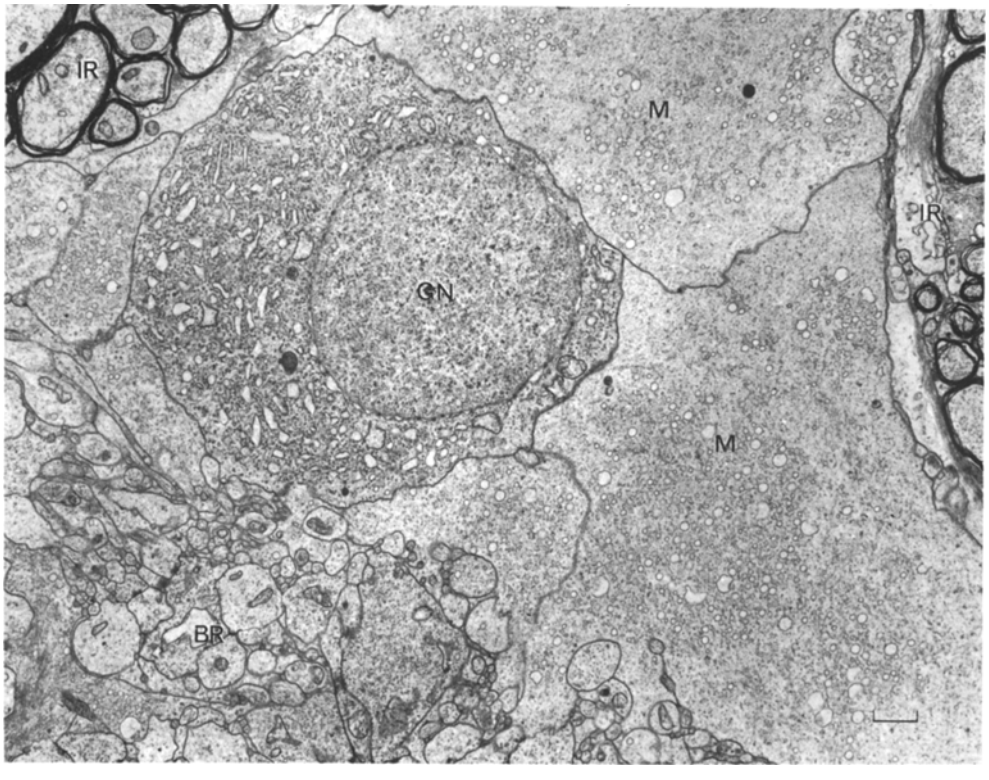

Fig. 3. Area of the inner plexiform layer and a ganglion cell after 60 min of anaesthesia. ×8,000. *GN* nucleus of the ganglion cell; *BR* inner plexiform layer; *IR* nerve fibres; *M* Müller's cell

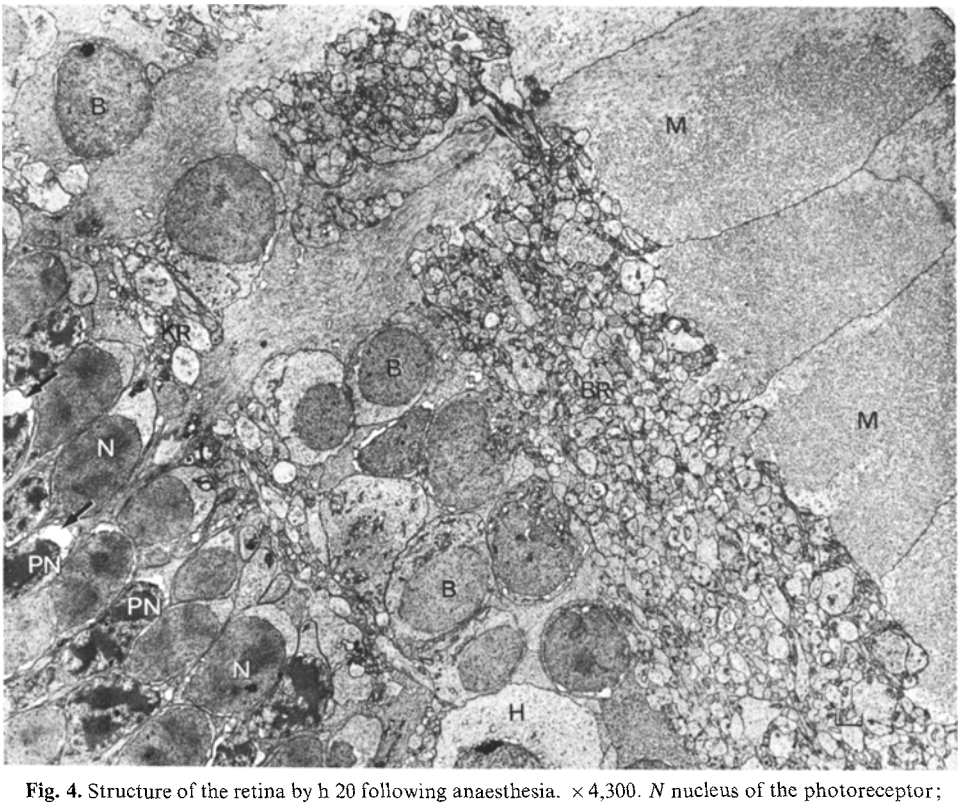

Fig. 4. Structure of the retina by h 20 following anaesthesia. ×4,300. *N* nucleus of the photoreceptor; *PN* pycnotic nuclei; *H* horizontal cell; *B* bipolar cell; *KR* external plexiform layer; *BR* internal plexiform layer; *M* Müller's cell; → perinuclear cisterns

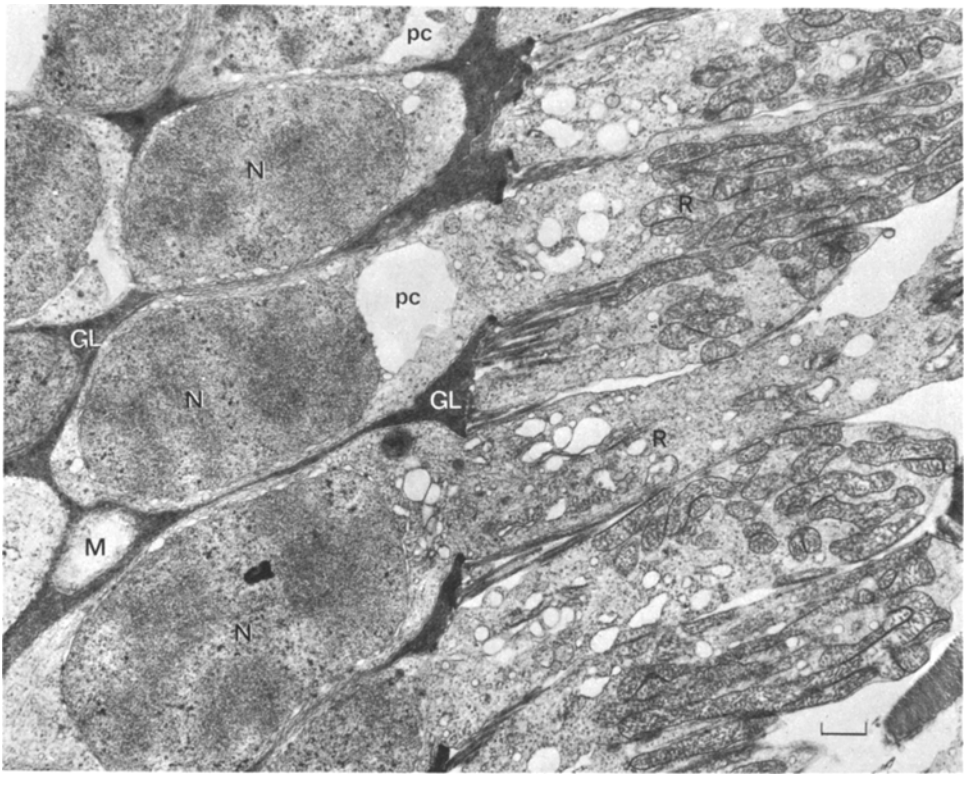

Fig. 5. Photoreceptor cells by h 48 following anaesthesia. ×8,000. *N* nucleus of the photoreceptor; *R* inner segment of the photoreceptor process; *pc* perinuclear cistern; *M* Müller's cell; *Gl* glycogen

others the filamentous structure were still noticeable. Glycogen accumulated in great masses in the Müller's cell processes, primarily at the height of the external nuclear and the external plexiform layers (Fig. 5).

Discussion

According to these investigations, no pathological changes of the retinal neurons could be detected immediately after etomidate anaesthesia of 60-min duration; only the structure of the Müller's cells was altered. One day following the anaesthesia, however, perinuclear cisterns and pyknotic changes developed in the nuclei of the photoreceptors, while the processes of the cells remained intact. The cells of the inner nuclear layer were vacuolised, too; nevertheless, the nuclei were not pyknotic. Neither the ganglion cells nor the plexiform and nerve fibre layers showed any alterations. At this time glycogen could not be seen in the Müller's cells and the structural cellular damage persisted. Two days following anaesthesia restitution of the damaged cells began. This was also true for the endoplasmic reticular system of the Müller's cells whose processes showed signs of increased glycogen accumulation at the height of the external nuclear and external plexiform layers.

In previous studies with ketamine anaesthesia, the neurons exhibited distinct, but transitory pathological changes following narcosis of 60-min duration. These changes corresponded to the formerly described hypoxic findings in the retina [27]. Each of the nuclear layers developed pathological alterations, besides damage to the processes of the photoreceptor cells. The Müller's cells were also more severely damaged. Three days following anaesthesia the changes almost entirely regressed and glycogen accumulated in great masses in every part of the Müller's cells.

Althesin, a steroid anaesthetic, did not induce alterations in the fine structure of the retina, the only abnormality being a great quantity of glycogen which was taken as a physiological sign of sleeping [3].

Vacuoles in the inner segment of the photoreceptor processes, perinuclear cisterns in the nuclear layers, condensation of the chromatin, pyknosis of the nuclei, and diminution of the glycogen content of the Müller's cells are characteristics of retinal hypoxia [11, 12, 17, 18, 19, 27, 38, 39, 40, 41, 42]. Oxygen and simultaneous glucose deprivation cause damage to the mitochondria, the Golgi-apparatus, the rough-surfaced endoplasmic reticulum as well as to the synapses [41]. Oxygen deprivation played the decisive role in this process, because glucose deprivation alone did not seem to be noxious.

The toxic alterations in the retina are manifest as swelling of the mitochondria, pyknosis of the nuclear layers, vacuolisation, development of inclusion bodies, disintegration of the vesicular structure of the Müller's cells, emptying of the glycogen, appearance of fibrils and distension of the Golgi-apparatus. Naturally, the entire spectrum of this damage may not always occur with different toxic agents [5, 14, 24, 27, 31, 32, 37, 43]. Glycogen accumulation might be taken as a sign of late toxic damage to the retina. Some of the drugs may cause destruction of all three neurons, while some of them cause isolated destruction of the glial cells [14, 34]. Destruction of the Müller's cells induces decay of the neurons in the course of time because of the lack of glial nutritive function.

In the case of etomidate anaesthesia pathological changes of the glial cells were found in the early phase of narcosis. Later on, alterations of the neurons developed which were mostly reversible, the damage to the inner nuclear layer certainly being reversible. The drug did not induce intraocular pressure elevation either under experimental or clinical conditions [4, 10, 29, 30, 33]; thus, this could be ruled out as a factor leading to ischaemia of the tissue. Changes in the systemic circulation during anaesthesia were also insignificant and, therefore, diminution of blood flow could also be excluded [4, 6, 8, 9, 13, 15, 22, 23, 36]. According to EEG examinations (Kugler et al.) [25, 26], etomidate belongs to the group of telencephalic hypnotics which do not influence the myelencephalic respiratory and circulatory centres. Burchardi [7] could not show any effect on the respiratory mechanics. Blood-gas results varied during its application, some authors observing hypoxia and some hypercapnia, but the two changes never occurred simultaneously [8, 13, 15, 16, 28] and Doenicke [9] could not show any blood-gas changes. According to the investigations of Renou et al. [35] the drug does not influence cerebral autoregulation, and several studies showed that there is no increase in oxygen utilisation [22, 23,

36]. Since changes in blood gases influence intraocular pressure to a lesser degree than cerebral blood flow, it is reasonable to exclude the causal effect of diminution of flow due to changes in respiration. One of the most outstanding signs of hypoxic retinal damage is the changes of the mitochondria which is easily seen in the outer segment of the photoreceptors. This phenomenon was never observed in etomidate anaesthesia. Furthermore, pathological changes were never seen in the immediate stages of narcosis; thus it can be suggested that the retinal changes in etomidate anaesthesia were not hypoxic in origin.

Jost et al. [21] studied cerebral glycolysis, the activity of the respiratory chain, and changes of metabolite concentrations under the influence of anaesthetics, including etomidate. They found that glycolysis was diminished, which meant a decrease in oxygen utilisation as well. If parallelism between cerebral and retinal metabolism is suggested, the former events might take also place in the retina. The results of the experiments with Althesin [3] would fit more easily into the concept of the cerebral and perhaps retinal metabolism-decreasing effect of anaesthetics, although there is no data on the cerebral effects of Althesin in the literature. The decrease in glycogen content following etomidate anaesthesia, however, argues against this metabolism-decreasing effect, it being more likely that the changes were caused by an independent retinotoxic mechanism. This view is supported by the observation that the pathological changes appeared one day following exposure. Also, the experiences of Oji and Holdcroft [30] suggest a new mechanism which is not, as yet elucidated. The authors were able to show that locally applied etomidate induced a decrease in intraocular pressure which persisted for as long as one week after the withdrawal of the drug.

The results of this study necessitate further studies of etomidate to elucidate the mechanism of the retinal damage. Further studies might also show whether the same deleterious effect was related to dose and/or duration of anaesthesia.

References

1. Anderson DR, Davis EB (1975) Sensitivities of ocular tissues to acute pressure-induced ischaemia. Arch Ophthal 93:267–274
2. Antal M (1979) Ketamine induced ultrastructural changes in the retina. Albrecht von Graefes Arch klin Ophthalmol 210:43–53
3. Antal M (in press) A retina ultrastrukturájának változása Althesin mononarkózis alatt. Morph Ig Orv Szemle (in Hung)
4. Antal M, Mucsi G, Gulyás J (in press) Etomidat okozta szemnyomás-változások. Szemészet (in Hung)
5. Babel J, Bischoff A, Spoendlin H (eds) (1970) Ultrastructure of the peripheral nervous system and sense organs. Thieme, Stuttgart
6. Brenken U, Karliczek G, Oldenziel H (1979) Etomidate und Dipidolor zur Narkoseeinleitung bei kardiochirurgischen Eingriffen. 16. Zentraleuropäischer Anästhesie-Kongreß, Innsbruck
7. Burchardi H (1979) Einfluß von Etomidate auf die Atemfunktion. Refresher Course. ZAK, Geneve 1977. Médecine et Hygiene, Genève
8. Colvin MP (1979) Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. Br J Anaesth 51:551–556
9. Doenicke A (1974) Etomidate, a new intravenous hypnotic. Acta anaesth belg 25:307–315
10. Eichelbauer B, Cunitz G (1977) Verhalten des intraokulären Druckes bei der Narkoseeinleitung mit Etomidate und Methohexital-Na. Prakt Anästh 12:384–389

11. Fehér J, Antal M (1978) Retinal changes in cardiac arrest. 5th Congress of the European Society of Ophthalmologists, Hamburg, 1976. Enke, Stuttgart
12. Fehér J, Antal M (1979) Ischemic retinal alterations in cardiac arrest. Ann Ophthal 11:909–913
13. Gooding JM (1979) Cardiovascular and pulmonary responses following etomidate induction of anaesthesia in patients with demonstrated cardiac disease. Anesth Analg 58:40–41
14. Haas K, Koniszewski G, Rix R (1979) Veränderungen in der äußeren plexiformen Schicht der Kaninchenretina nach langer Gabe von Vincristin. Albrecht von Graefes Arch klin Ophthalmol 211:23–33
15. Hempelmann G (1974) Influence of Althesine and etomidate on blood gases (continuous pO_2-monitoring) and hemodynamics in man. Acta anaesth belg 25:402–412
16. Hempelmann W, Hempelmann G, Piepenbrock S (1977) A comparative study of blood gases and hemodynamics using the new hypnotic etomidate, CT 1341, methohexitone, propanidid and thiopentone. In: Etomidate. Doenicke A (ed) Anaesthesiology and Resuscitation, Vol 106. Springer, Berlin Heidelberg New York
17. Johnson NF (1974) Effects of acute ischaemia on the structure of the rabbit retina. Trans Ophthal Soc UK 94:394–405
18. Johnson NF (1976) Electron microscopy of acute retinal ischaemia in the rabbit and study of the pattern of recovery. In: Vision and Circulation. Cant JS (ed), H Kimpton, London
19. Johnson NF (1977) Retinal glycogen content during ischaemia. Albrecht von Graefes Arch klin Ophthalmol 203:271–282
20. Johnson NF, Grierson I (1976) Post-mortem changes in the rabbit retina. Acta Ophthal 54:529–541
21. Jost U (1980) Beeinflussung der cerebralen Glycolyse und Atmungskettenoxidation (dem neuronalen energieliefernden Stoffwechsel) durch Thiopental, Flunitrazepam und Etomidate im steady state einer standardisierten Inhalationsnarkose. Anaesthesist 29:12–17
22. Karliczek GG, Brenken U, Agnew M (1980) Narkoseeinleitung mit Etomidate und Piritramid bei Patienten mit Koronarsklerose oder Klappenfehlern. Anaesthesist 29:1–11
23. Kettler D (1974) Hämodynamik, Myokardmechanik, Sauerstoffbedarf und Sauerstoffversorgung des menschlichen Herzens unter Narkoseeinleitung mit Etomidate. Anaesthesist 23:116–121
24. Koniszewski G, Rix R, Brunner P (1976) Histologische und elektronenmikroskopische Befunde an der Kaninchenretina nach Gabe von Vincristin. Albrecht von Graefes Arch klin Ophthalmol 199:147–156
25. Kugler J, Doenicke A (1977) Classification des hypno-analgésiques. Rev EEG Neurophysiol 7:112–116
26. Kugler J, Doenicke A, Laub M (1977) The EEG after etomidate. In: Etomidate. Doenicke A (ed) Anaesthesiology and Resuscitation, Vol 106. Springer, Berlin Heidelberg New York
27. Kuwabara T, Cogan DG (1961) Retinal glycogen. Arch Ophthal 66:680–688
28. Marquort F, Waubel H, Brückner JB (1977) The influence of R 26490 (etomidate sulfate) on ventilation and gas exchanges. In: Etomidate. Doenicke A (ed) Anaesthesiology and Resuscitation, Vol 106. Springer, Berlin Heidelberg New York
29. Oji EO, Holdcroft A (1979) The ocular effects of etomidate. Anaesthesia 34:245–249
30. Oji EO, Holdcroft A (1979) Effect of etomidate on the intraocular pressure in rabbits. Exp Eye Res 29:429–435
31. Orzalesi N, Calabria GA, Grignolo A (1970) Experimental degeneration of the rabbit retina induced by iodoacetic acid. Exp Eye Res 9:246–253
32. Orzalesi N, Grignolo A, Calabria GA (1967) Experimental degeneration of the rabbit retina induced by sodium fluoride. Exp Eye Res 6:165–170
33. Pannarale MR (1978) Etomidate e pressione endoculare. Boll Oculist 57:421–426
34. Pedersen OØ, Karlsen RL (1979) Destruction of Müller cells in the adult rat by intravitreal injection of D,L-amino-adipic acid. Exp Eye Res 28:569–575
35. Renou AM (1978) Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth 50:1047–1051
36. Sonntag H, Kettler D (1977) Effect of induction agents on myocardial hemodynamics: influence on the choice of induction agents for patients with ischemic heart disease. In: Proceedings of the VIth Congress of Anaesthesiologists, Mexico City 1976. Hülsz E, Sánchez-Hernández JA, Vasconcelos G, Nunn JN (ed). Excerpta Medica, Amsterdam Oxford

37. Sorsby A, Harding R (1960) Experimental degeneration of the retina. V. Fasting and metabolic accelerators in degeneration produced by sodium fluoride. Br J Ophthal 44:213–224
38. Tsacopoulos M (1976) Studies of experimental retinal focal ischaemia in miniature pigs. In: Vision and Circulation. Cant JS (ed) H Kimpton, London
39. Vassileva PI, Dabov SB (1976) Changes in the glycogen content and the electroretinogram in retinal ischaemia experimentally-induced in rabbits. In: Vision and Circulation. Cant JS (ed) H Kimpton, London
40. Wassilewa P, Hockwin O, Korte I (1975) Glycogen concentration changes in retina, vitreous body and other eye tissues caused by disturbances of blood circulation. Albrecht von Graefes Arch klin Ophthalmol 199:115–200
41. Webster HF, Ames A (1965) Reversible and irreversible changes in the fine structure of nervous tissue during oxygen and glucose deprivation. J Cell Biol 26:885–909
42. Weiss H (1972) The carbohydrate reserve in the vitreous body and retina of the rabbit's eye during and after pressure ischemia and insulin hypoglycemia. Ophthal Res 3:360–371
43. Yoo JH (1976) Responses of Müllers-cells of rabbit retina in experimental siderosis. Jap J Ophthal 20:149–168

Received July 23, 1980