Experimental occlusion of the central artery of the retina. IV: Retinal tolerance time to acute ischaemia*

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SUMMARY Ophthalmoscopic, fluorescein angiographic, electrophysiological, and morphological studies on 63 eyes of rhesus monkeys with acute transient experimental occlusion of the central artery of the retina (OCAR) showed that the retina suffered irreparable damage after ischaemia of 105 minutes but recovered well after ischaemia of 97-98 minutes. The tolerance time of the brain to acute transient ischaemia is many times shorter than that of the retina. The metabolism of ischaemic neurones (in the retina and brain) is discussed with a view to explaining this difference, and also the various factors possibly responsible for the retina's longer tolerance of ischaemia, as compared to the brain.

Occlusion of the central artery of the retina (OCAR) is a true ophthalmic emergency, when every minute that elapses increases the chances of death of the retina. It is therefore absolutely essential to know how long it takes for acute retinal ischaemia to produce irreversible damage. Much of the confusion about this length of time is due to the many conflicting claims reported in anecdotal clinical case studies and in animal experiments, so that it is not at all surprising that in spite of the considerable interest which this subject has attracted no definite conclusion has been reached so far.

Previous studies

CLINICAL CASE REPORTS

Table 1 comprises most of the available reports in the English literature plus a few from other languages. Recovery of retinal function is said to take place after an ischaemia of anything from 10 minutes to as much as 36 hours. In addition there are 2 more reports in which slow recovery of vision after OCAR has been described. Story⁹ in 1899 described 2 such cases. A 35-year-old man suddenly lost vision in the left eye to light perception (LP) which improved to counting of fingers (CF) and to

6/24 after 16 and 24 days respectively, and to 6/9 and 6/6 after 43 and 112 days respectively, with an ophthalmoscopically normal fundus. And a 39-year-old woman, who suddenly lost vision in the left eye, recovered to CF in 7 days and to 6/9 in 32 days. Werner¹⁰ described a 27-year-old syphilitic woman who, when seen 14 days after a sudden loss of vision in the left eye, was considered to have classical ophthalmoscopic findings of OCAR and doubtful LP. One week later the vision was LP in the superior nasal quadrant. One week after that she suddenly lost vision in the right eye with OCAR and was found to have doubtful LP in the right eye and CF in the left eye. The visual acuity in the left eye improved to 6/9 42 days after the occlusion and in the right eye to 6/12 and 6/9 14 and 20 days after the occlusion.

EXPERIMENTAL STUDIES

These are summarised in Table 2. There is a good deal of inconsistency in the results obtained, one report alleging irreversible retinal damage within 3 minutes, while in others much longer was needed. The relevance of those findings to clinical OCAR in man is open to criticism because of the following limitations in most of these studies.

Some of the animals used in these studies are not suitable for such an investigation; for example, rabbits have virtually no retinal circulation and the retina depends almost entirely for its nutrition on the choroidal circulation; cats have no central artery of the retina. The retinal ischaemia in these experiments was mostly produced by raising the

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Table 1 Previous clinical case reports of OCAR and recovery of vision

Author	Year	No. of eyes	Duration of ischaemia (hours)	Visual recovery to	Age	Cause of OCAR
Mauthner ¹	1868	1	1½	Normal	—	Embolus
Wood-White ²	1882	1	About 1	6/6	31	Embolus
Mules ³	1888	1	1	Normal	21	Embolus in inferior retinal artery
Wagenmann ⁴	1898	1	1/6	Normal	—	Spasm
Young ⁵	1932	1	About 36	Normal	70	Embolus
Orr and Young ⁶	1935	1	19¼–27	Normal	—	Embolus in inferior temporal branch artery
Watson ⁷	1969	1	1/4	6/5	78	Arteriosclerosis
		1	1/2	6/9	53	Embolus
		2	2 and 2½	6/4	25	Orbital fracture
		1	4½	6/12	18	Not known
		1	6	6/36	65	Mild hypertension
		1	8	HM	75	Arteriosclerosis
		1	9	6/18	64	Thrombotic thrombocytopenic purpura
		1	13	6/36	42	Embolus
		1	14	6/18	18	Not known
		1	15	CF	65	Not known
		1	24	HM	26	Not known
		1	27	6/60	75	? Giant cell arteritis
		1	36	6/60	66	Mild hypertension
Younge and Rosenbaum ⁸	1978	1	About 2½	Normal	21	Embolus

CF = counting fingers. HM = hand motion.

Table 2 Previous experimental reports of acute retinal ischaemia and retinal tolerance time to ischaemia

Author	Year	Experimental animal	Experimental method to produce retinal ischaemia	Method used to evaluate retinal integrity	Tolerance time
Turnbull ¹¹	1948	Rat	Animal centrifugation	Histology	<3 min
		Rat	Section of CAR	Histology	<4–5 hr
		Rat	Asphyxiation of animal	Histology	<3 min
Smith and Baird ¹²	1952	Rat	↑ IOP 100 mmHg	Histology	15 min
Popp ¹³	1955	Rabbit	↑ IOP 160 mmHg	ERG	>60–<75 min
Reinecke <i>et al.</i> ¹⁴	1962	Cat	↑ IOP 125 mmHg	Histology	<1½ hr
Böck <i>et al.</i> ¹⁵	1963	Human	↑ IOP 200 mmHg	ERG	>60–<120 min
Fujino and Hamasaki ¹⁶	1967	Squirrel	↑ IOP to systolic BP	ERG and histology	60–<90 min
		Monkey			
Hamasaki and Kroll ¹⁷	1968	Squirrel Monkey	Nylon suture looped around CAR in orbit	ERG and optic tract discharges	>90–<210 min
Foulds and Johnson ¹⁸	1974	Rabbit	↑ IOP 10 mmHg above systolic BP	ERG and light and electron microscopy	Up to 1 hr
Johnson ¹⁹	1974				
Vassileva and Dabov ²⁰	1976	Rabbit	↑ IOP to supra-arterial level	ERG and retinal glycogen content	About 50 min
Shay and Ames ²¹	1976	Rabbit	Retina incubated in media lacking oxygen and glucose		40 min

BP = blood pressure. Hr = hours. IOP = intraocular pressure. Min = minutes.

intraocular pressure to supra-arterial levels, which not only stops the retinal circulation but also stops the choroidal circulation—the latter almost never occurs in the usual clinical OCAR in man. In almost none of these studies was there any systematic evaluation of the retinal circulation by fluorescein angiography. Finally, the retinal integrity was evaluated by electroretinography (ERG) and/or by histology. Our studies have clearly shown that ERG is not an entirely reliable technique for assessing retinal function after OCAR because it does not give us any information about the functional status of the ganglion cells or of most of the inner retina, which is essentially the area involved by OCAR in man.

Materials and methods

Our studies of experimental OCAR in 63 eyes eliminate these limitations by: (1) use of the rhesus monkey, which has a central retinal artery, retinal vasculature, retina, and other anatomical and physiological features identical to man's; (2) transient clamping of the central artery of the retina (CAR) at its site of entry into the optic nerve without interfering with the rest of the ocular circulation;²² (3) systemic evaluation of the retinal circulation by fluorescein angiography before, during, and after clamping the CAR and by fundus ophthalmoscopy;²² (4) evaluating the functional integrity of the retina not only by ERG but also by visual evoked response (VER), because the latter gives us information about the function of the retinal ganglion cells, optic nerve fibres, and the rest of the retina⁹ and in a number of animals even by testing the vision;²³ (5) using not only histological but also electron microscopic techniques to evaluate the morphological status of the retina;²⁴ (6) and finally, by using a large sample size (63 eyes) to discover the various biological variations in the response of retina to ischaemia.

Detailed accounts of our findings are given in the earlier papers of this series.^{22–24} Briefly these are as follows:

Ophthalmoscopic findings.²² These are summarised in Table 3. OCAR for up to 97–98 minutes did not produce significant permanent retinal or optic nerve damage except in 2 eyes (with OCAR for 75 minutes) which may represent a normal biological variation in response. However, OCAR for 105 minutes or more always produced irreversible permanent marked retinal and optic nerve damage.

Fluorescein angiographic findings.²² In all but 2 eyes with retinal ischaemia for up to 97–98 minutes the retinal circulation, after unclamping the CAR, remained perfectly normal throughout, with retinal

Table 3 *Ophthalmoscopic appearance at the end of the follow-up period*

Duration of ischaemia (minutes)	Follow-up period (weeks)	No. of eyes	Retina	Optic disc	Retinal vessels
16–20	12–22	11	Normal	Normal	Normal
75	1/2, 4, 22	3	Normal	Normal	Normal
		2	Atrophic ++	Atrophic* ++	Normal
90	12–14	3	Normal	Normal	Normal
97–98	17–19	4	Normal	Slight pallor* +	Normal
105	13–16	4	Atrophic ++/ normal-looking	Atrophic* +++	Narrow
134–138	13–14	3	Atrophic +++	Atrophic* +++	Narrow
270–280	13–14	3	Atrophic +++	Atrophic* +++	Narrow

*Started after 2 weeks and maximum by 3 weeks.

Table 4 *Pattern of recovery of ERG and VER after unclamping CAR*

Duration of ischaemia (minutes)	No. of eyes	Recovery time for	
		Normal ERG	VER present
90	6	5–40 minutes	1–3½ hours
97–98	8	15–60 minutes	Approx. 4 hours
102	2	1, 2 hours	2½, 4½ hours
	2	1½, 3 hours	No recovery
105	2	17 minutes, 3 hr	> 3½ hours–< 1 day
	4	5, 45, 75 min, 1 day	No recovery
135	6	2½, 3, 4 hours, 1 day, 1 day, ?	No recovery
270	5	b-Wave ½ normal	No recovery

capillaries normally outlined and no other angiographic abnormality. In eyes with retinal ischaemia of 105 minutes or longer and in 2 eyes with 75 minutes' OCAR the retinal capillaries and retinal pigment epithelium showed some atrophic changes.

Electrophysiological findings.²³ These are summarised in Table 4. These show that the ERG recovered to the normal level in all eyes with OCAR of up to 135 minutes, and the b wave was half normal with normal a wave in eyes with OCAR for 270 minutes. In contrast to these findings, the VER recovered to normal in all eyes (except 2) with OCAR up to 97–98 minutes and in 2 of the 4 eyes with OCAR for 102 minutes; in the rest of the eyes, i.e., 2 eyes with OCAR for 75 minutes, 2 eyes with 102 minutes, and all with 135 and 270 minutes' ischaemia, the VER did not recover. All the animals with OCAR for 97–98 minutes in their right eye and followed up

for 3–4 months had their normal left eye completely closed by a tarsorrhaphy; after this procedure the animals were found to behave normally, as if their vision had recovered in the right eye.

Morphological findings.²⁴ Light and electron microscopic studies revealed that OCAR for 105 minutes or longer resulted in irreversible damage to the inner part of the retina, including the inner two-thirds of the inner nuclear layer; the photoreceptors and outer part of the retina, including the outer one-third of the inner nuclear layers, were normal. The retina showed regional differences in susceptibility to ischaemia, the macular region being the most susceptible, the perimacular region less so, and the peripheral retina least of all. Differential susceptibility to ischaemia was also observed among various organelles and cells of the retina. Among the cytoplasmic organelles the mitochondria were found to be most susceptible, with microtubules and endoplasmic reticulum less so in descending order; the nuclei were the least susceptible of all. Among the retinal cells the ganglion cells were more susceptible than the bipolar cells, with Müller cells and astrocytic glia less susceptible, and the pericytes and endothelial cells of the vessels relatively resistant to ischaemia. The optic nerve showed atrophic degeneration of the nerve fibres. Eyes with OCAR for 97–98 minutes or less showed no appreciable permanent morphological damage in the retina and optic nerve.

Discussion

The data on our above-mentioned 4 types of findings^{22–24} were analysed separately by the 3 different investigators and collated only at the end. It was most interesting that all of us arrived at virtually the same conclusion, that is, the retina can tolerate acute ischaemia for up to 97–98 minutes with full recovery in all eyes, with rare exceptions. All eyes with OCAR for 105 minutes or more suffer irreparable damage. Half of the eyes with 102 minutes' OCAR recovered visual function.

Our findings conflict with many of the anecdotal clinical reports (Table 1) and experimental reports (Table 2). The clinical reports by Mauthner,¹ Wood-White,² Mules,³ Wagenmann,⁴ and 2 by Watson⁷ (Table 1) agree with our findings. One of us (S.S.H.) saw a patient with OCAR who consulted an ophthalmologist and had his normal vision restored by a massage and paracentesis about 90 minutes after the onset of the visual loss. The patient has been followed up for 2½ years with normal visual fields and a visual acuity of 6/6. The present study casts serious doubt on the case reports

of recovery of vision many hours and even days and weeks after the onset of OCAR. It could be argued that in these patients there was sufficient residual retinal circulation after OCAR to protect against ischaemia; we investigated this topic particularly. Our findings were that there was no well-defined correlation between the amount of small residual retinal circulation and the severity of retinal damage. This subject is discussed in detail in Part I of this series.²² The discrepancies between the present study and some of the previous experimental studies (Table 2) may be due to the several limitations in those studies discussed above.

TERMINOLOGY

In connection with this subject it may be useful to distinguish the many terms used in the literature, e.g., survival time, recovery time, and tolerance or endurance time. Our definitions are as follows:

Survival time is the period during which after the onset of ischaemia there is still demonstrable function. (This has been reported as 4–5 minutes in rabbits¹³ and 5–15 seconds in man;^{25,26} this was not investigated in the present study.)

Tolerance or endurance time is the period of ischaemia after which function recovers completely, e.g., 97–98 minutes in our study.

Recovery time is the time taken by the retina to recover normal function after the restoration of normal circulation; this varied with the duration of ischaemia in our studies (Table 4), being about 4–4½ hours in eyes with 97–102 minutes' OCAR.

In the literature these terms are used interchangeably and confusingly.

COMPARISON OF THE TOLERANCE TIME TO ISCHAEMIA BETWEEN THE RETINA AND THE BRAIN

The findings of the present study also raise another very important question. In the brain permanent neuronal damage has been reported after ischaemia of 3½ (in cats²⁷) to over 6 minutes (in dogs²⁸), though recovery of some neuronal functions in cats had been reported 30 minutes after cardiopulmonary arrest.²⁹ In man cardiac arrest lasting for 3 minutes leads to permanent brain damage at 37°C, but at 28°C the brain withstands cardiac arrest for up to 7½ minutes.³⁰ Bourne³¹ concluded that cerebral ischaemia of up to 2 minutes is followed by full recovery, but even a small extension of this time produces permanent damage. Meyer³² recorded extensive neuronal necrosis in man following cardiac arrest under anaesthetic with ischaemia of 1 minute.

However, according to Garcia *et al.*^{33,34} although it has been held traditionally that ischaemia of a few

minutes' duration is lethal to brain tissue, the statement is not based on data derived from experimental scrutiny. Their biochemical and ultrastructural observations suggest that not only can mammalian brain seemingly endure prolonged incomplete ischaemia, but a serious breakdown of the system occurs only roughly 5 hours after the initial stroke.

It could well be argued that OCAR alone in man and primates represents an incomplete ischaemia of the retina, because the choroidal circulation remains normal and is not comparable to the complete global ischaemia of the brain. Experimental increase of intraocular pressure to above the arterial blood pressure level stops all intraocular circulations and produces 'global' retinal ischaemia and is comparable to the 'global' brain ischaemia. However, the available evidence (Table 2) does indicate that the retinal tolerance time to acute ischaemia is almost identical whether the ischaemia is produced by clamping the CAR alone (with normal choroidal circulation) or by raising the intraocular pressure to above the level of the arterial blood pressure (with arrest of both retinal and choroidal circulations).

In spite of the above mentioned findings by Garcia and others, clinical findings in man with complete global brain ischaemia and irreparable loss of cortical functions after about 3–7 minutes^{27 28 30–32} indicate that the tolerance time of the brain to ischaemia seems to be many times shorter than the retina's, though it has a similar neural structure. Naturally the question arises, why? To understand some of the factors responsible for this difference, it is essential to understand the mechanism of ischaemic damage to the neural tissue, which has been summarised very well by Dixon.³⁵

METABOLISM OF ISCHAEMIC NEURONES

For normal functioning, neural tissue requires 2 cardinal nutrients: glucose and an adequate supply of oxygen. There is considerable evidence that ATP and creatine phosphate (CrP) are the major high-energy compounds generated from respiration and glycolysis.³⁶ Ischaemia rapidly depletes the neurone of its stores of these compounds, thereby depriving the cells of the chemical energy so essential for maintaining both the electrical and synthetic activity of the cell. Aerobic oxidation can effect the synthesis of about 20 times as much ATP as is formed during anaerobic catabolism of the same quantity of sugar. Within about 10 seconds after the onset of complete ischaemia the oxygen of the brain is entirely consumed, leading to a sudden switch to anaerobic metabolism. It is supposed that the loss of consciousness in ischaemia is due to the fact that the cells do not have an adequate supply of

energy under anaerobic conditions. The most critical initial loss, therefore, is lack of oxygen and not of glucose.

METABOLISM OF ISCHAEMIC NEURONES IN THE RETINA

All the available studies on the subject have been conducted in rabbits only. Weiss³⁶ investigated the glycolysis in retinal ischaemia in rabbits. He found that rabbit retina normally has 0.05 mg glucose and 0.35 mg glycogen and the vitreous has 1.0–1.1 mg glucose and no glycogen, i.e., the glucose content of the vitreous is nearly 3 times higher than that of the retina. However, Wassilewa *et al.*³⁷ did find glycogen in the vitreous of rabbits (mean value of 350 μ mol/100 g in vitreous as compared to 2780 μ mol/100 g in the retina). In retinal ischaemia produced by raising the intraocular pressure to supra-arterial blood pressure levels Weiss³⁶ described the following changes: 'in the first 15–20 minutes of pressure ischaemia, the carbohydrate was taken up exclusively from the glycogen reserve of the retina. During the period of 20–40 minutes the glycogen content of the retina showed only a diminished decrease, about 30% of the value during the first 20 minutes. The reduction of the vitreous body glucose began simultaneously. It ranged within approximately the same limits as the utilisation of retinal glucose during the first 15–20 minutes. During the 40- to 70-minute period after the start of pressure ischaemia, the glucose reserve of the vitreous body was the only energy source for the glycolytic activity of the retina. Experiments extending beyond 70 minutes showed only slight sugar utilisation. When the experiment was extended to 2 hours, no significant difference was demonstrable between values after 90 and 120 minutes'.

If glucose-utilisation is taken as the indicator of anaerobic glycolysis in this experiment, then anaerobic glycolysis decreased during prolonged ischaemia. If it is assumed to be 100% in the first 15–20 minutes, it is 80–90% from 20–40 minutes, 70% from 40–60 minutes, 50% at 70 minutes, and 20–30% at 90 minutes' ischaemia. On restoration of retinal circulation after 1 hour of ischaemia the glucose of the vitreous remained constantly low in the first 30 minutes. One hour after the end of ischaemia it was replenished 80–90%, and an hour later it was normal. However, retinal glycogen was not replenished in this period, and only 2 days after the ischaemia did the glycogen reserve of the retina begin to renew itself; it was normal 24–36 hours after that. Intravenous administration of glucose did not affect the replenishment of retinal glycogen content in rabbits. These studies of Weiss³⁶ in rabbits showed that glucose taken anaerobically

from the vitreous is used up exclusively by the retina. He concluded that it is not the retinal glycogen but the glucose of the vitreous that must be regarded as the most important energy carrier in the retinal ischaemia lasting more than 20 minutes, and the exhaustion of the anaerobic glycolysis is one of the most essential factors determining the limits of tolerance time of the rabbits' retina. Ames and Gurian³⁸ and Webster and Ames³⁹ in incubated isolated rabbit retina found that either anoxia or glucose withdrawal alone produced less marked electrophysiological and electron microscopic changes than those produced by deprivation of both. Kaskel *et al.*⁴⁰ found that several intermediates of glycolysis were changed in their concentrations after pressure ischaemia of rabbit retina, indicating a shift from aerobic to anaerobic breakdown of carbohydrate. The high consumption of glucose in anaerobic glycolysis results in higher consumption of glycogen.^{37 40} Vassileva and Dabov²⁰ found in rabbits that after 60–70 minutes' ischaemia complete replenishment of retinal glycogen did not occur, indicating irreversible change in the activity of enzymes which synthesise glycogen from blood glucose; they emphasised the great significance of glycogen in the retinal metabolism. Johnson⁴¹ found no glycogen in the Müller cells after 45–60 minutes' ischaemia in rabbits. Wassilewa *et al.*³⁷ found reduction in vitreous glycogen as well, though much less than in the retina. Oberhoff and Hockwin⁴² found that ATP content of the retina was decreased by 40% after 1 hour's pressure ischaemia in cat and rabbit eyes, and they assumed glycogen to be an energy store for the retina.

The suggestion that NAD⁺ concentrations may be of rate-limiting significance in the retina as well as in the brain is indicated by a related study of experimental microembolism in the miniature pig by Bardy and Tsacopoulos.⁴³ They found, histochemically, that oxidation reduction systems utilising NAD were not detectable following ischaemia. These authors also found a pH drop in the retina to 7.19 and then to 7.01 after 10 minutes. They ascribed this to diffusion into the retina of lactate accumulated in the vitreous. They speculated that this decrease in pH results in decrease in the activity of the phosphofructokinase system, a rate-limiting step in glycolysis, and eventually to cessation of cell function.

Although much more remains to be learned about the biochemical metabolic changes in the ischaemic retina, it is certain that an adequate supply of glucose and oxygen is vital for the normal functioning of the retina and that glycolysis is essential for its survival.

FACTORS RESPONSIBLE FOR MUCH LONGER TOLERANCE TIME TO ISCHAEMIA BY THE RETINA THAN THE BRAIN

Probably the following factors have an important role.

(1) The findings of Weiss³⁵ and others^{37–43} may help to explain the fact that the tolerance time of the retina is many times longer than that of the brain during ischaemia. The brain has very scanty stores of intracellular glucose and depends entirely on the blood circulation to supply constantly not only oxygen but also glucose. In contrast to that, in the retina, the situation is very different because (i) there is an ample store of glucose and glycogen, (ii) in addition, the vitreous's glucose content is nearly 3 times that of the retina, and (iii) probably the most important factor is that the major part of glucose and oxygen (80% and 60% respectively in pigs, and 80% of oxygen in cats⁴⁴) consumed by the retina ordinarily is delivered by the choroidal vessels.⁴⁵ This gives the retina self-sufficiency in glucose, and to some extent in oxygen, for a much longer time than the neurones in the brain. Weiss³⁶ found that in the rabbit retina, after 1 hour of ischaemia, there was still 0.15 mg of glycogen in the retina (0.35 mg in normal retina) and 0.60–0.65 mg glucose in the vitreous (1.0–1.1 mg normally). However, other similar studies in rabbits reported complete loss of glycogen in the retina following 45–60 minutes of ischaemia.^{20 37 41} The immediate loss of function in the retina (blindness) and in the brain (loss of consciousness) seem to be due to the deprivation of oxygen and show no difference between the 2 tissues.

(2) No-reflow phenomenon in ischaemic brain: The no-reflow phenomenon is the most accepted current view explaining the irreversible brain damage after a transient brain ischaemia. Development of marked oedema of the neural tissue in acute ischaemia is a well-known phenomenon. When this occurs in the brain, firstly the rigid cranial cavity cannot accommodate the extra volume produced by the oedema, and, secondly, since the brain as an organ is composed of thick, solid tissue, the deeper parts of the brain have no place to expand to in the surrounding solid, swollen tissue. Those 2 factors combine to cause obliteration of the microvasculature (since the vascular structures are the only pliable tissue which will yield and collapse as the neural tissue expands). This secondary vascular occlusion effectively prevents the return of the blood supply even if the circulation is quickly restored. The other factors which probably contribute to the no-reflow phenomenon in the brain are increased blood viscosity resulting from a shift of fluids from the extracellular to intracellular phase,⁴⁶ intravas-

cular sludging and clotting,⁴⁷ postischaemic rise in intracranial pressure,⁴⁸ and postischaemic hypotension.⁴⁹ Ames *et al.*⁴⁶ and others have shown that this local perfusion defect on restoration of circulation to the neural tissue (which may still be viable) produces irreversible damage.

The retina, on the other hand, is a very thin membrane set in surroundings which can accept oedema easily and regulate its pressure without compromising the retinal microvasculature, so that the phenomenon of no-reflow does not exist in the ischaemic retina. Hence the striking difference in tolerance times between the brain and the retina. It is conceivable that, if the neural tissue of the brain had a similarly favourable environment it could survive for a much longer time than it does.

(3) The other factor responsible for the retina's much greater tolerance of ischaemia than the brain's may be the difference in susceptibility to ischaemic damage by different types of neurones, as seen in the brain.²⁷ It is possible that the retinal neurones are more resistant to ischaemia than the neurones in the brain. Our studies²⁴ have shown that within the retina itself there is a differential susceptibility to ischaemic damage (*vide supra*). One of the possible reasons for the differential susceptibility between the different neurones may be the amount of protein turnover in a particular neurone. It has been shown that ischaemia inhibits cerebral protein synthesis,^{50,51} and this could explain the early and selective enzyme loss in certain areas of the brain. If an area has a high rate of protein turnover, it would be more susceptible to ischaemia. This would be especially true if increased proteolysis occurred, catalysed by lysosomal proteases released by cell destruction.⁵²

(4) Importance of the vitreous as a reserve source of oxygen for the retina: It could be argued that oxygen in the vitreous may play some role in the prolonged tolerance of the retina to ischaemia. Dr Albert Alm (Uppsala, Sweden), from various studies by him and his group (Anders Bill, Per Törnquist) on cats and pigs, calculated for us the amount of oxygen in the vitreous, which is most probably 2.4 μ l, corresponding to about 100 nmol oxygen (A. Alm, personal communication). Since the oxygen consumption of one pig retina *in vivo* is about 300 nmol/minute, the calculated oxygen in the vitreous could support normal retinal metabolism for about 20 second only. This would indicate that the vitreous can be disregarded as a significant source of oxygen in OCAR.

These are some possible reasons for the difference in the tolerance of ischaemia between the retina and brain, but there is much more to be learned before we can explain this mystery satisfactorily. This is an

important subject, because a better understanding of it could give us clues to increasing the tolerance of ischaemia not only in the retina but also in the brain, and thus help us to buy time for resuscitating these organs after acute ischaemia.

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