Correspondence

Axoplasmic transport and ischaemic disc swelling

Sir, I was interested to read the paper by McLeod et al. on 'Role of axoplasmic transport in the pathophysiology of ischaemic disc swelling', but was considerably upset by the references to myself and my work, several of which were distorted and some downright untrue. The following are a few examples:

1. Anterior ischaemic optic neuropathy (AION) and cilioretinal artery occlusion. In the last paragraph of the paper the authors stated:

(a) 'Hayreh\(^2\) chose to illustrate the concept of a segmental ION (ischaemic optic neuropathy) with a patient in whom vision was totally lost from PCA (posterior ciliary artery) occlusion but in whom no accumulation of axoplasm occurred in that half of the disc that was contiguous with a large cilioretinal infarct. The disc appearance, however, depended on the underlying nature of ischaemic disc swelling, and the use of the term "segmental ION" in such a case seems unwarranted'.

I presume the authors are referring to the right eye of a 71-year-old woman with temporal arteritis, AION, cilioretinal artery occlusion, and no perception of light (see Fig. 17a-i).\(^2\) At no point did I make any mention or implication that this eye had 'segmental ION'—that would have been utterly absurd. In fact this eye did not have segmental AION. To label an eye with AION and no light perception as having segmental AION would represent complete ignorance of the basic facts about AION.

(b) They further added: 'Hayreh\(^3\) has also described examples of so-called "sectoral ION" contiguous with infarcts of inner retina supplied by cilioretinal arterioles. It is likely, however, that these were cases of pure cilio-retinal artery occlusion and that the disc swelling represented an accumulation of axoplasm resulting from obstruction of retrograde axoplasmic transport. Such an opaque accumulation of axoplasm in the optic nerve head after cilioretinal artery occlusion (and also after hemisphere branch retinal artery occlusion and CRA occlusion) should not be designated "ION" even though the disc swelling is of a fundamentally similar nature. I cannot help resenting the implication that I do not know how to differentiate a cilioretinal artery occlusion alone from that where such an occlusion is a part of AION.

2. Peripapillary pigment epithelial change in AION. The authors attributed the following to me:

(a) 'Part of the disc swelling was recently attributed to infarction of the peripapillary pigment epithelium'.\(^2\) I have never made such an absurd statement. Actually what I stated was: 'During the first 2 to 3 weeks after the onset of acute AION, a whitish lesion continuous with the infarct of the optic nerve head is seen, involving the peripapillary region for a variable distance; this is in all probability degenerate pigment epithelium in this region caused by the ischaemia of the underlying peripapillary chorioid'.\(^3\) It is hard to understand how McLeod et al. would have misread this statement written in very simple English. Evidently this is one of the examples of deliberate distortions in this paper.

(b) Another totally unfounded statement reads: 'It is significant, however, that identical pigmentary changes (in the peripapillary region) were present around the optic discs of the unaffected eyes in each of the cases presented by Hayreh in support of his contention'. This is simply not so. Firstly, my publications\(^2\) give no picture of the fellow unaffected eye, so that I cannot understand where they got such an impression. Secondly, in my work\(^2\) referred to McLeod et al. in 24 of 25 cases (apart from minor age-related peripapillary pigment epithelial degeneration) there was no comparable degenerative change in the fellow unaffected eyes. Even in the one with a significant peripapillary pigment epithelial degenerative change in the unaffected eye, the eye with AION when seen 2 days after the onset of blindness had much less pigment epithelial degeneration than was seen later on, and furthermore fluorescein angiography later on revealed more marked degenerative changes in the eye with AION than in the unaffected eye. Since publishing the series referred to above\(^3\) I have now seen and studied in detail over 300 cases with AION, fully documented, and peripapillary pigment epithelial degenerative changes are present much more frequently and more extensively in the eye with AION than in the fellow unaffected eye.

(c) The authors further stated that: 'The absence of peripapillary pigment epithelial change adjacent to ischaemic nerves after PCA occlusion in this study further denies the general concept proposed by Hayreh.' It is worth noting that McLeod et al.'s conclusions are based on a total of 6 eyes (5 eyes followed for 4 days and one eye for 7 days only), which is a very small number, followed for far too short a period for pigment epithelial degeneration to develop (which takes at least 2–3 weeks).

Moreover, the PCA occlusion was performed in young, healthy monkeys with extremely good potential for the rapid development of collateral circulation, and the eyes developed hypotony which further aids significantly in intraocular vascular filling. To extrapolate from such an experimental situation to lesions seen with vascular occlusion in old, atherosclerotic and arteriosclerotic human patients is quite unjustified, as I have frequently stressed (see p. 15–18).\(^2\)

3. Altitudinal visual field defect in AION. The authors stated that: 'Hayreh\(^4\) has repeatedly suggested that such an altitudinal hemianopia results from occlusion of a main PCA supplying the upper half of the choroid and optic disc'. This is a complete distortion of what I have stated. Of the 2 papers by me\(^4\) cited by McLeod et al., in the one published in 1970\(^4\) (during the very early stages of my studies on PCA circulation in rhesus monkeys) I stated: 'It is difficult to give a definite explanation why the upper part of the choroid and optic disc circulation should be far more commonly involved than the inferior part. One can only surmise'.\(^4\) Based on the information available up to that time, in monkeys only (no human studies were conducted at that stage), I...
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speculated that it could be due to the alitudinal distribution by the PCA. In the work published in 1975, when human studies had been done, although I did not rule out the above possibility occasionally (and I have since seen it occur in a few of my patients with AION), I stated: 'More commonly, where the main posterior ciliary arteries supply the nasal and temporal halves of the choroid, non-filling of the watershed zone between the posterior ciliary arteries, above or below the optic disc, would produce a filling defect in the corresponding half of the optic disc. Such filling defects were seen in the present study . . . . However, I have no explanation as yet for the higher frequency with which the superior compared to the inferior watershed zone is involved.' This is not a 'repeated suggestion'.

The authors have also attributed to me: 'It has been suggested, however, that the typical visual field defect resulting from such occlusion is a hemianopia whose vertical border passed through the blind spot . . . . We have been unable to confirm such a field defect clinically'. This, again, is untrue; firstly, I never stated that a vertical hemianopic defect was the typical visual field defect of AION, and, secondly, I have seen vertical hemianopic field defects clinically in 8-4% of 162 eyes with AION seen up to about 3 years ago.

4. Filling of temporal peripapillary choriocapillaris after lateral PCA occlusion. Another slight but significant distortion is McLeod et al.'s statement that 'delayed filling of the temporal choriocapillaris was noted in only a minority (my italics) of the animals studied by Hayreh and Baines'. The actual figure was one-third out of 85 eyes studied in that series, certainly a minority but not the insignificant number implied by the authors, compared with their series composed of a total of only 11 eyes. No doubt their findings would have changed if they had taken the time and trouble to accumulate a significant series of cases. Whereas generalisations are always dangerous, they are especially so in dealing with the ocular vasculature, where the natural variations are so wide (almost like the finger prints!).

5. Segmental AION. Anyone with any worthwhile clinical experience of AION cases is well aware that the vast majority of eyes with AION have a segmental visual field loss, clearly indicating segmental ischaemic damage in the optic nerve head, i.e., segmental AION. As far as I can judge from the description in the paper, McLeod et al. do not believe in the existence of a segmental AION, presumably reflecting their lack of experience of clinical AION.

The authors make some other statements which are open to question, such as the one that the peripapillary choroidal supply to the optic nerve head is 'more prominent in monkeys than in man'. This conclusion is based on a histological study with serious limitations when applied to the in-vivo situation, and is not supported by a number of human studies, including my fluorescein angiographic experience of the optic nerve head circulation in health and disease in hundreds of human eyes over the past, about 15 years. I find no basis for the statement that the vascular pattern of the optic nerve head in man is different from that in rhesus monkeys.

My statements on AION are based on an experience of over 300 cases of AION investigated in detail and prospectively followed for years in our Ocular Vascular Clinic, of detailed studies in about 170 eyes of rhesus monkeys (followed for up to half a year) with experimental PCA occlusion of various types over the last 10 years, and of extensive studies on the morbid and physiological anatomy of the blood supply of the optic nerve and rest of the eye over the past 25 years. I find it sad that McLeod et al. feel impelled to make dogmatic statements and equally dogmatic rebuttals of statements which others have or have not actually made, based on less than I week's study of 11 eyes! The factor most disturbing to me, however, is the careless and even wanton misquotation of words which when I published them, were chosen with the utmost care to reflect the state of my knowledge at the time. Where I have speculated, I have stated that this was speculation. When new information is available, our views change and we should be prepared to let go our cherished theories, and even to admit in print that we were wrong. This I have steadfastly tried to do. In the field of research we are learning every day, and should strive above all things to keep our minds open—to the views of our scientific colleagues as well as our own findings—to distinguish fact from speculation, and the statistically significant from that which is provisional and incomplete. I can only urge Mr McLeod and his colleagues to do likewise. To do any other is to do a disservice to themselves, to their colleagues and above all to scientific research.

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References

Sir, We thank Dr Hayreh for his interest in our recent paper and welcome the opportunity to discuss controversial aspects of acute ischaemic optic neuropathy (ION). Dr Hayreh has made many contributions to the
literature on this subject, culminating in his extensive monograph. The discussion to our paper centred on his work and commented on aspects relevant to our recent experimental and clinical studies. We note with regret that Dr Hayreh dismisses many of our views simply as signs of ignorance and clinical inexperience.

Before discussing the specific points raised by Dr Hayreh we should emphasise that there are fundamental differences in our respective approaches to the study of the neuronal damage resulting from an ischaemic insult. This is reflected both in our dynamic analysis of the pathophysiology of ION and in our use of nomenclature. In essence, after examining in detail the topography of the cytoplasmic damage induced by experimental occlusion of the posterior ciliary arteries (PCAs) we have discriminated the subtle variations in ophthalmoscopic appearance between different parts of clinical lesions, and our use of mechanistic terms is based on empirically demonstrated phenomena. Thus, we have clearly distinguished the primary ischaemic insult from secondary areas of biological amplification such as the axonal swellings resulting from interrupted axoplasmic flow at the lamina cribrosa. By examining the generation of the ischaemic insult, rather than trying to categorise it by its consequences, we have inevitably used relatively few animals.

In answer to the points raised:

1a. The lesion concerned was described as ‘partial ION’ (p. 59) (a term used synonymously with segmental ION elsewhere in the text), with disc swelling and infarction involving ‘only a part of the optic disc’ (p. 32). The case was also referred to in a section discussing the choroidal circulation in sectoral ION (p. 73).

1b. The suggestion that the disc swelling in these cases represents ION conflicts with our demonstration that the characteristic opaque prelaminar swelling in ION necessitates continuing orthograde axoplasmic transport in the retinal nerve fibre layer subsequent to retrolaminar infarction. Provided that Dr Hayreh can explain this discrepancy, his resentment is justified.

2a. We fail to understand how our paraphrase represents a ‘deliberate distortion’ either of the quoted statement or of the following (p. 32): ‘Stereoscopic examination revealed a white mass lying deep to the superficial transparent nerve-fibre layer of the optic disc; the mass looked like a white infarct of the prelaminar region that had merged with an almost equally white zone around the disc, presumably infarcted pigment epithelium, so that disc margins could not be delineated’. While applauding the simple English, we disagree with this interpretation. In our view the white swelling of the prelaminar region (including the superficial nerve-fibre layer) results from accumulated axoplasm (not infarction or oedema), while infarction of the peripapillary pigment epithelium contributes to the clinical stereoscopic appearance of ION only very rarely, if ever.

2b. Our statement is based on personal knowledge and photographic documentation of the 2 examples used by Dr Hayreh to substantiate his hypothesis. Changes similar to those alleged to have been a consequence of outer retinal infarction were present in both fellow unaffected eyes. Furthermore, in both cases the pre-existing peripapillary and parapapillary degenerative changes in the affected eyes were visible at the onset of the ischaemic lesions (though somewhat masked by the overlying swelling of the nerve-fibre layer). These changes can be seen in the published plates and undoubtedly represent ‘a variable degree of peripapillary degenerative halo—complete or partial—as is not rare’ (p. 69). Dr Hayreh’s new statement that the pre-existing degeneration in one of these eyes increased after ION does not accord with the facts (as can be demonstrated by detailed examination of the original photographs). Nevertheless, if there is other evidence to substantiate Dr Hayreh’s hypothesis, then we await publication with interest.

2c. We were unable to find any histopathological sign of ischaemia in the pigment epithelium adjacent to optic nerves with retrolaminar infarcts. Taken in isolation we agree that this observation is not conclusive, but it does contribute to the mass of evidence denying Dr Hayreh’s interpretation of the ophthalmoscopic appearance in ION. Our findings also accord with Dr Hayreh’s own statement that peripapillary outer retinal damage (diagnosed funduscopically) occurs extremely infrequently after experimental PCA occlusion (p. 16).

3a. At no point did we elaborate on the excess clinical incidence of inferior over superior altitudinal hemianopia. The quoted remark related to the following statements (not speculations): ‘Altitudinal hemianopias of prechiasmal origin and without any retinal lesion are caused by occlusion of the main PCA which supplies that half of the disc and choroid’. When the PCAs supply the upper and lower halves of the choroid and the optic disc, occlusion of one of these would result in altitudinal hemianopia. Sometimes the PCAs supply the upper and lower parts of the choroid and the optic disc with a horizontal boundary line. Occlusion of one of the two main PCAs produces an altitudinal field defect with no retinal changes (our italics). The only published justification for this view has been the angiographic appearance in 2 monkeys following orbitotomy and central retinal artery occlusion; we can only remind Dr Hayreh of his own warnings about extrapolation from the experimental to the clinical situation.

Regarding the ‘watershed’ theory, we believe it is inappropriate to consider the arterial supply to the anterior optic nerve and disc in terms of watershed zones, since multiple circulations with rich anastomoses converge at this point. We should also point out the dangers of invoking focal prelaminar ischaemia from the angiographic findings in segmental ION. Accumulated axoplasm causes significant masking of fluorescence (as in cotton-wool spots and papilloedema) so apparent nonfilling of the swollen disc-sector should be interpreted with caution.

Regarding vertical hemianopias, our statement related to the illustrated vertical subdivision and hemiacclusion of the PCA supply (Fig. 11).

4. We consistently demonstrated late dye filling of the temporal peripapillary choroid within 1 hour of temporal short PCA occlusion in the 11 published eyes, and also in other eyes in which temporal short PCA occlusion was combined with central retinal vascular occlusion (unpublished data). This contrasts with the experience of
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Dr Hayreh, who stated that there was ‘complete absence’ of such filling in one publication but described similar findings to ours in ‘about one-third’ (out of 31 rather than 85 eyes) in another report. In these circumstances we feel that ‘a minority’ is a reasonable guestimate of Dr Hayreh’s experience.

We feel it is unlikely that this discrepancy in our respective findings is due to the smallness of our series and natural variations in the pattern of ocular vasculature between animals. It is possible, for example, that it reflects the better general circulatory condition of our monkeys after the orbitotomy compared with those operated on by Dr Hayreh; experimental vascular occlusions are produced during general anaesthesia and a variable degree of surgical shock which may impair collateral flow.

5. At no point did we refute the existence of segmental ION; indeed we published 1 such case in our paper (‘Fig. 11). However, we believe that ‘segmental PCA occlusion’ is not proved as the cause of the common clinical picture consisting of inferior altitudinal hemianopia, constriction of the peripheral superior visual field, and generalised optic disc swelling with the predominant accumulation of axoplasm in the upper half. This might equally well reflect a general diminution in PCA supply with collateral circulation maintaining the viability of part of the inferior retrolaminar neural tissue (analogous to cilioretinal sparing in central retinal artery occlusion).

Regarding the ocular vasculature of monkeys and man, we have not studied the relevant comparative anatomy (but have rather referred to the views of researchers whose work we respect), so no further comment from us is indicated.

Finally, regarding the number of animals in our experiment, we would reiterate our belief that valid conclusions can be drawn from a small series provided the experiment is well designed and the findings are definitive and reproducible. Dr Hayreh occluded the PCAs in 85 (or 170) eyes, yet in none was histopathology of the acute lesion in the anterior optic nerve reported. Despite this provisional and incomplete information he came to the following dogmatic conclusion (not speculation): ‘Since the entire optic nerve head (except for the superficial nerve-fibre layer) is supplied by the PCAs, occlusion of the PCAs produces massive infarction in the optic nerve head’ (p. 79). Our investigation shows that this is not the case, thus separating fact from fiction in experimental PCA occlusion. It also casts serious doubts on the assertion in Dr Hayreh’s letter that segmental ION ‘clearly indicates segmental ischaemic damage in the optic nerve-head’. We have disproved or at least de-emphasised the prelamina region as the site of infarction, and have demonstrated that the primary ischaemic lesion involves the retrolaminar optic nerve (where, it should be noted, a segmental arterial supply is said to be less well defined).

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References

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Obituary

Edwin Gordon Mackie, MA, FRFPs, FRCS Glas, DOMS

Edwin Gordon Mackie, who was an honorary ophthalmic surgeon to the United Sheffield Hospitals, died on 30 August after a brief illness. He was 84.

He graduated at St Andrew’s University, where his undergraduate career was interrupted by the first world war, during which he served as a sergeant in a machine gun corps. In the second world war he was promoted colonel and commanded an RAMC unit overseas. Mackie was appointed honorary consultant at Sheffield in 1927 to the Royal Hospital. He is remembered as an imaginative teacher by his students. Later in life he became president of the North of England Ophthalmological Society and the Faculty of Ophthalmology. He was a keen attender at meetings of the Ophthalmological Society of the United Kingdom and was honoured by life membership. In 1955 he gave the Middlemore Memorial Lecture.

His retirement was a happy one with his second wife, who survives him together with a son and 2 daughters. Outdoor sport in the way of shooting and an interest in heraldry filled his days and kept his intellect keen to the end.

S.J.H.M.