CORRESPONDENCE

Myopia in diethylstilboestrol exposed ambylopic subjects

EDITOR,—Diethylstilboestrol (DES) is a synthetic, non-steroidal pseudo-oestrogen. It was prescribed for many pregnant women between 1948 and 1971 with the intention of preventing spontaneous abortions and premature delivery.1 Embryonic neural tissue is particularly sensitive to gonadal hormones which play a vital part in axonal growth.2 “Estrogen and androgen appear to induce inherent neural programs in which androgen increases neurite arborization and the receptive field of individual cells, increasing the likelihood for intercellular communication, while estrogen actually induces this communication, in the form of new androgen receptor sites.”3 High myopia rates in opposite sex twins has been attributed to ocular development in the unusual hormonal environment.4 DES, among various oestrogenic compounds, is the most effective competitive inhibitor for binding oestrogen receptors in the developing monkey brain.5

The purpose of this retrospective study was to assess the effect of DES exposure in utero on ocular development and explore its relation with refractive status associated with amblyopia. The DES exposed subjects were recruited by placing a notice in the newsletter “DES Action News”, asking for people with amblyopia who had been exposed to DES in utero to provide their visual acuity and refractive error measurements. Thirteen DES exposed amblyopic subjects responded. The refractive errors of 10 are shown in Table 1. The refractive status of the DES exposed group of amblyopes was compared with 255 amblyopic patients with no history of DES exposure. Thirty nine amblyopic subjects with a myopic spherical equivalent in both eyes were identified in the group of 255 patients (15.3%). It was assumed that this represents the true frequency of myopia among the non-DES exposed amblyopic population. The probability that 10 out of 13 amblyopic subjects will be myopic in a sample of amblyopes was found to be $p = 3.4 \times 10^{-15}$ using the exact binomial test.

Table 2 compares the spherical equivalents for both eyes of a group of bilaterally myopic subjects with amblyopia to the DES exposed amblyopes. It is noted that the average and median values indicate that there is a higher degree of myopia among the DES exposed group. These findings suggest that prenatal exposure to DES, with isolated estrogen receptors in developing neural tissue, may be a factor in the appearance of myopia among some amblyopic patients who were born in the two decades beginning in 1950. Similarly, prenatal exposure to other pseudohormones which are present in some plants and pesticides, may also affect ocular development.6

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Cataract and season of birth

EDITOR,—Harding and van Heyningen1 have done a well designed and testing a tentative hypothesis relating to a possible link between the season of birth and the prevalence of [one type of] cataract, but also of quoting from a preprint I sent them. The latter showed that there was a statistically significant variation of the season of birth is to be observed in the prevalence of mixed nuclear and posterior subcapsular cataracts both in an immigrant Indian population and among natives of the British Isles.

The latter observation does not seem to have caught the authors’ eyes, and I made no comment for the conditions described in their paper. While my results may not be valid for Oxfordshire, they refrained from defining the types and distribution of cataracts on which their analysis is based. Consequently we do not know whether Oxfordshire patients with mixed nuclear and subcapsular cataracts may not perhaps share the observed characteristic, and their results are merely confounded by the addition of those patients who do not.

R A WEALE
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Reply

EDITOR,—We are grateful for Professor Weale’s comments on our attempt to test his hypothesis that the risk of cataract may depend on the season of birth. Our results indicated that season of birth was of no importance in an Oxfordshire population,1 whereas he reported an excess of cataract patients, with some types of cataract, born in the spring on the Indian subcontinent.2 The two studies differed in both design and the populations studied. Our results were based on the dates of birth of 723 cataract patients and 1217 controls who took part in two case-control studies of cataract in Oxfordshire.1,2 The controls were from both hospital sources and the community (age and sex registers of general practitioners). Each control group was age and sex matched to the cataract group. Dates of birth of all subjects were recorded. All subjects in Professor Weale’s study were outpatients at Moorfields Eye Hospital. There was an excess of births reported on New Year’s Day in those born on the Indian subcontinent which was dealt with by partial elimination. The Moorfields patients were divided into three ethnic groups, British, Indian, and Caribbean. There were no controls so he attempted to account for the known seasonal variation in birth rate by using a published monthly birth index. Our use of controls from exactly the same area matched for age and sex would seem preferable. There was a seasonal variation in births of patients in Oxfordshire but it corresponded to that in controls. The different designs could explain the different results.

Professor Weale found an excess of pooled cataract patients born in the spring on the Indian subcontinent. This excess was due to an excess in those with a combination of nuclear and subcapsular cataracts. The same type of cataract was associated with birth in both the summer and December in “native British”, again compared with a birth index, assumed to represent a British control population. In his letter he suggests that we may have lost a significant effect because the critical subtype was diluted by all other cataracts, but that did not occur in our study, indeed the highest level of significance was found when he pooled all types of cataract (p=0.00032 compared with 0.0168 for the nuclear plus posterior subcapsular combination). This of course provides the greatest numbers (362). The major disadvantage of subdivision is that the numbers dwindle away and thus the power of the study is diminished. It is not surprising that novel risk factors have mostly been identified in studies on mixed cataracts.3

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RUTH VAN HEYNINGEN
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Table 1 Refractive errors of 10 amblyopic subjects who had been exposed to DES in utero

<table>
<thead>
<tr>
<th>Right eye</th>
<th>Sphere</th>
<th>Cylinder</th>
<th>Axis</th>
<th>Left eye</th>
<th>Sphere</th>
<th>Cylinder</th>
<th>Axis</th>
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</thead>
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<td>Cylinder</td>
<td>Axis</td>
<td>Sphere</td>
<td>Cylinder</td>
<td>Axis</td>
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<td></td>
</tr>
<tr>
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<td>+3.50</td>
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<td>+1.75</td>
<td>14</td>
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<td></td>
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<td></td>
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</tr>
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</tbody>
</table>

Table 2 Statistical comparison of spherical equivalents for both eyes of two groups of amblyopic subjects

<table>
<thead>
<tr>
<th>DES exposed amblyopes (n=10)</th>
<th>Amblyopic without DES (n=39)</th>
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</thead>
<tbody>
<tr>
<td>Spherical equivalent</td>
<td>Spherical equivalent</td>
</tr>
<tr>
<td>Minimum myopia</td>
<td>−14.63</td>
</tr>
<tr>
<td>Maximum myopia</td>
<td>−1.00</td>
</tr>
<tr>
<td>Average</td>
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<tr>
<td>Standard deviation</td>
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<tr>
<td>Standard error</td>
<td>0.78</td>
</tr>
<tr>
<td>Median</td>
<td>−5.38</td>
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</table>

Correspondence, Obituary, Notices


Osteo-odontokeratoprosthesi surgery

EDITOR—We wish to point out some inaccuracies portrayed by the media on osteo-odontokeratoprosthesis (OOKP) surgery offence at our hospital. In 1996, we performed the awareness of KPro surgery, but we can be grateful to the media for increasing public interest in the OOKP technique in Britain to the future prospects. Refract Corneal Surg 1995; 193-4.

This latter conclusion seems to be unlikely since local retinal vasosconstruction is supposed to be influenced much more by the local ET-1 concentration than the elevation of the systemic venous ET-1 level. If elevated ET-1 concentrations in the peripheral circulation induce RVO, one would suppose it to be experienced in many RVO cases—for example, in normal pressure glaucoma, which is frequently associated with elevated plasma ET-1 values. On the contrary it is primary open angle glaucoma with elevated intraocular pressure and mild to moderate systemic hypertension that is frequently associated with RVOs. Both of these conditions are characterised by normal ET-1 concentrations. These clinical considerations suggest that the direct influence of peripheral ET-1 levels on the retinal microcirculation is very unlikely.

The authors' main conclusion that RVOs cause a systemic elevation of venous ET-1 concentrations seems to be relevant. However, the authors should have shown some more data to exclude a few factors with a potential influence on their results. One should take into account the severity of systemic hypertension between hypertensive patients and the uncomplicated hypertensive control subjects? Severe hypertension may have supported the authors' hypothesis on the role of systemic ET-1 levels. In fact, we concluded that the elevated systemic ET-1 levels are likely to be a consequence of the occlusive event.

We also agree that establishing a precise relation between ET-1 concentrations and time elapsed from RVO diagnosis may indeed be crucial in understanding the role that ET-1 plays in RVOs. Similar to what has been observed in patients with myocardial infarction,7 it is quite possible that, immediately following the occlusion, ET-1 concentrations may have been elevated to a greater extent, and that ischaemic neovascular complications ensued only in those patients in whom ET-1 levels persisted above a certain threshold level. By inducing experimentally ischaemic branch RVOs, Pournaras26 and colleagues27 showed that ischaemic retinal areas are always hypoxic, yet progression to neovascularisation occurs in only about 50% of cases. They postulated the need for persist-
ence of critically low PO2 levels for neovascularisation to develop. We suggest that elevated intraretinal ET-1 levels in the area of the occluded vessel may be at least one of the critical factors in causing the low PO2 retinal levels. A self reinforcing cycle may be taking place locally, in which ET-1 release by endothelial cells following RVO could diffuse in the vicinity of the occluded vessel to the abluminal side of neighbouring pericytes and induce capillary non-perfusion. The ensuing ischaemia could further enhance ET-1 release by retinal endothelial cells, maintaining and extending retinal non-perfusion. Long lasting hypoxia can induce upregulation of vascular endothelial growth factor (VEGF) receptors, VEGF overexpression, and lead to retinal neovascularisation. Recent experimental evidence supports the possibility that elevated ET-1 levels occur in retinal neovascularisation and precede VEGF upregulation. Since ET-1 also exerts a dose dependent mitogenic effect on retinal pericytes, it is tempting to speculate that persistence of ET-1 about a putative threshold level could perpetuate the ischaemic condition and contribute, hand in hand with VEGF, to the complex chain of events that leads to retinal neovascularisation in RVOs. These hypotheses, although intriguing and well substantiated, await further verification.

The potential effect of confounding factors on ET-1 determinations is also very important. Maximal care was placed in selecting the outpatient population. In fact, nearly half of the population we examined clinically was excluded from the study because it did not meet our stringent inclusion criteria. Lerman and colleagues have shown elegantly that ET-1 elevations are proportional to the severity of the associated vasculopathy. Other than the RVO itself, we have no evidence to suggest that the control group of uncomplicated hypertensive subjects may have had less severe hypertensive vascular damage than the investigated RVO population. In addition, if this was the case, it would contradict the hypothesis that the observed peripheral ET-1 elevations reflected the local retinal event, on which both Dr Hólló and we seem to agree. All but one of our RVO hypertensive patients (No 18 in the study) were on either mono- or multitherapy for hypertension (range 1–3). Pre-RVO medications included angiotensin converting enzyme (ACE) inhibitors (n=6), calcium channel blockers (n=4), nitrates (n=3), diuretics (n=2), and β blockers (n=1). Although not exactly matched, uncomplicated hypertensive subjects had a similar medication pattern. It has been suggested that ACE inhibitors may reduce ET-1 plasma levels in some disease states. Our RVO patients on ACE inhibitors, however, did not have ET-1 concentrations (15.05 (SD 5.2) pg/ml) significantly different from the mean ET-1 levels observed in the study population (14.22 (4.6) pg/ml) for all RVO patients, yet significantly greater than both normals and uncomplicated hypertensives (p<0.01). The same applied to the RVO patients on calcium channel blockers (16.82 (4.52) pg/ml). We also plotted ET-1 concentrations as a function of the number of hypertensive medications (data not shown), which failed to reveal significant correlations (R = 0.30, p = 0.16; R = 0.26). All seven RVO patients with a history of elevated intraocular pressure were on topical β blockers, but, as addressed in our paper, they had ET-1 plasma levels superimposable to those of RVO patients with normal ocular pressure. Therefore, there is no indication that our measurements may have been influenced by either systemic or topical treatment regimens. These additional considerations, prompted by Dr Hólló’s acute remarks, further confirm our conclusion that the elevated ET-1 levels are most likely accountable for by the retinal occlusive event.

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OBITUARY

Ronald Francis Lowe, MB, ChB (Melb), MD (Melb), FRCS (Eng), FRACS, FRACO, FCOPH (UK), PHC (Melb), 1913–98

Ronald Francis Lowe was devoted to the very highest standards of ophthalmology. Born in 1913, he died at the age of 84 in March 1998 after a lifetime of service to the Royal Victorian Eye and Ear Hospital and his profession. A tall and imposing man, he also showed a driving rain upon the window. He described how he first came to practise ophthalmology at a time when it was not considered a specialty in its own right. He explained his quest to understand angle close glaucoma; how he listened to his patients, how he recorded his observations, how he reflected on possible mechanisms. He described his travels to China and the regional differences in the presentation of glaucoma and how well received he was by his Asian colleagues, eager to learn from this Australian who physically towered over them.

Increasing age had not dimmed his enthusiasm, his knowledge of the literature, or his curiosity about glaucoma in all its forms. He enjoyed great devotion from his patients and was much admired by his peers. His first wife, Lois, died in 1985 and in 1987 Ron married Zena, a fellow ophthalmologist and great companion, with whom he shared many and varied interests. He is survived by Zena, his son, Richard, and his younger brother, Rupert. They can take comfort from the fact that his influence and contributions will long endure.

JULIAN RAIT
Director, Glaucoma Units, Centre for Eye Research Australia, University of Melbourne, The Royal Victorian Eye and Ear Hospital, Melbourne, Australia
Residents’ Foreign Exchange Programme
Any resident interested in spending a period of up to one month in departments of ophthalmology in the Netherlands, Finland, Ireland, Germany, Denmark, France, Austria, or Portugal should apply to: Mr Robert Acheson, Secretary of the Foreign Exchange Committee, European Board of Ophthalmology, Institute of Ophthalmology, University College Dublin, 60 Eccles Street, Dublin 7, Ireland.

7th Rotterdam International Skull Base Day/Esser course
The 7th Rotterdam International Skull Base Day/Esser one day course on orbital and peri-orbital lesions will be held on 23 January 1999. Further details: Mrs K Sipman, PO Box 1738, 3000 DR Rotterdam, Netherlands. (Tel: +31 10 40897787; fax: +31 10 4362762).

Ophthalmic technologies
The 9th Ophthalmic Technology Conference will be held on 23–24 January 1999 during the International SPIE symposium on biomedical optics. Further information: The SPIE Organisation, PO Box, Bellingham, WA 98227-0010, USA. (Fax: (+1) 360-647-1445; email: www:spie.org/info/pw)

Laser eye injuries
A conference on the epidemiology, prevention, diagnosis, and therapy of laser eye injuries will be held in San Jose, California on 25–26 January 1999 during the International SPIE symposium on biomedical optics. Further information: The SPIE Organisation, PO Box, Bellingham, WA 98227-0010, USA. (Fax: (+1) 360-647-1445; email: www:spie.org/info/pw)

Office of Continuing Medical Education
The 21st Annual Wilmer Institute’s Current Concepts in Ophthalmology will be held on 4–9 February 1999 at the Hyatt Regency Cerromar Beach Hotel, Dorado, Puerto Rico. Further details: Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Medical Education, Turner 20/720 Rutland Avenue, Baltimore, MD 21205, USA. (Tel: (410) 955-2317 or (632) 925-3789; fax: (632) 924-6550; email: cmenet@som.adm.jhu.edu)

Ophthalmological Congress, University of Creteil
An international symposium on the macula will be held on 26–27 March 1999 at the Ophthalmological Clinic, University of Creteil. Further details: Professor G Soubrane, Chef de Service, Clinique Ophthalmologique Universitaire de Creteil, Centre Hospitalier Intercommunal, 40 Avenue de Verdun, 94010 Creteil, France. Fax: 01 45 17 52 27.

Leonhard Klein Award 1999
The Leonhard Klein Award 1999, valued at DM30 000, will be given for innovative, scientific works in the field of development and application of microsurgical instruments and microsurgical operating techniques. It can be conferred on an individual as well as a group of researchers. The work must be submitted in either English or German by 31 March 1999. Further details: Stifterverband fur die Deutsche Wissenschaft eV, Herrn Peter Beck, Postfach 16 44 60, D-45224 Essen, Germany.

12th Annual Meeting of German Ophthalmic Surgeons
The 12th annual meeting of German Ophthalmic Surgeons will be held on 10–13 June 1999 at the Meistersingerhalle, Nürnberg, Germany. Further details: MCN Medizinische Congress-Organisation Nürnberg GmbH, Weilandstrasse 6, D-90419 Nürnberg, Germany. (Tel: ++49-911-3931621; fax: ++49-911-3931620; email: doerflinger@mcn-nuernberg.de)

XII Congress European Society of Ophthalmology
The XII Congress European Society of Ophthalmology will be held in Stockholm, Sweden on 27 June–1 July 1999. Further details: Congress (Sweden) AB, PO Box 5819, S-114 86 Stockholm, Sweden. (Tel: +46 8 459 66 00; fax: +46 8 661 91 25; email: soc@congresx.se; http://www.congresx.com/soe/)

4th Meeting of the European Neuro-Ophthalmology Society
The 4th meeting of the European Neuro-Ophthalmology Society will be held on 29 August–2 September 1999 in Jerusalem, Israel. Further details: Secretariat, 4th Meeting of the European Neuro-Ophthalmology Society, PO Box 50006, Tel Aviv, 61500, Israel. (Tel: 972-3-514000; fax: 972-3-5175674/972-3-5140077; email: Eunos99@kenes.com)

Ophthalmological Clinic, University of Creteil
An international symposium on the macula will be held on 1–2 October 1999 at the Ophthalmological Clinic, University of Creteil. Further details: Professor G Soubrane, Chef de Service, Clinique Ophthalmologique Universitaire de Creteil, Centre Hospitalier Intercommunal, 40 Avenue de Verdun, 94010 Creteil, France. Fax: 01 45 17 52 27.

Jules François Prize
The 2000 Jules François Prize of $100 000 for scientific research in ophthalmology will be awarded to a young scientist who has made an important contribution to ophthalmology. All topics in the field of fundamental and/or clinical research in ophthalmology will be considered. The application should be sent jointly with a curriculum vitae, the list of all publications, and three copies of the candidate’s 10 most relevant publications to Jules François Foundation Secretary, Professor Dr M Hanssens, Dienst Oogheelkunde, de Pintelaan 185, B-9000 Gent, Belgium. Deadline for applications 31 December 1999.
Myopia in diethylstilboestrol exposed amblyopic subjects

PHILIP LEMPERT

Br J Ophthalmol 1999 83: 126
doi: 10.1136/bjo.83.1.126

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