CORRESPONDENCE

Myopia in diethylstilboestrol exposed amblyopic 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 action potentials and dendritic spines.”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 253 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 x 10^-6" 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, which blocks oestrogen 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.7

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REFERENCES

Cataract and season of birth

EDITOR,—Harding and van Heyningen1 have done this to me by suggesting 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 the hypothesis was valid.2

The major disadvantage of subdivision is that the critical subtype was diluted by all other cataracts, but 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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Table 1 Refractive errors of 10 amblyopic subjects who had been exposed to DES in utero

<table>
<thead>
<tr>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>Cylinder</td>
</tr>
<tr>
<td>−11.5</td>
<td>−2.50</td>
</tr>
<tr>
<td>−8.00</td>
<td>+2.50</td>
</tr>
<tr>
<td>−7.25</td>
<td>+1.75</td>
</tr>
<tr>
<td>−7.25</td>
<td>+3.25</td>
</tr>
<tr>
<td>−6.00</td>
<td>+0.50</td>
</tr>
<tr>
<td>−5.50</td>
<td>−3.50</td>
</tr>
<tr>
<td>−3.00</td>
<td>+2.25</td>
</tr>
<tr>
<td>−2.50</td>
<td>+3.00</td>
</tr>
<tr>
<td>−6.25</td>
<td>+2.75</td>
</tr>
<tr>
<td>−4.00</td>
<td>+5.00</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>DES exposed amblyopes (n=10)</th>
<th>DES exposed amblyopes (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium equivalent</td>
<td>−14.63</td>
<td>−18.00</td>
</tr>
<tr>
<td>Maximum myopia</td>
<td>−1.00</td>
<td>−0.13</td>
</tr>
<tr>
<td>Average</td>
<td>−5.33</td>
<td>−2.67</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>3.94</td>
<td>2.86</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.78</td>
<td>0.33</td>
</tr>
<tr>
<td>Median</td>
<td>−5.38</td>
<td>−1.50</td>
</tr>
</tbody>
</table>

REFERENCES
Osteo-odonto-keratoprosthesis surgery

Editor,—We wish to point out some inaccuracies portrayed by the media on osteo-odonto-keratoprosthesis (OOKP) surgery offered at our institution. In 1996, we performed our first OOKP operation that was televised as a BBC “Tomorrow’s World” programme. In the programme, the operation was described as “new”. This was not true as the technique of OOKP surgery was invented by the late Benedetto Falcinelli in Rome in 1964.1


Christopher Liu independently surveyed Falcinelli’s results in 1994.2

The “newness” of the operation related only to the introduction of Falcinelli’s OOKP technique into Britain for the first time. We had the opportunity to offer the launch of the Falcinelli technique in Britain to the BBC, when Professor Falcinelli and his team were invited to assist with the first few operations. In the event, Professor Falcinelli was keen to do surgery himself but the television programme had not portrayed him as being the lead surgeon.

Colleagues abroad informed us recently that abridged versions of the programme claiming that Falcinelli was the only place in the world where OOKP surgery is offered. This is not true. There are many types and techniques of artificial corneas or keratoprostheses (KPro). An international KPro study group exists and has met every 3 years for exchange of ideas and experience.

We can be grateful to the media for increasing the awareness of KPro surgery, but we must make it clear that there have been unfortunate inaccuracies as detailed above.

Christopher Liu
Andrea Sciscio
CITY-SCUFTI
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Plasma endothelin-1 concentrations in patients with retinal vein occlusions

Editor,—I read with interest the article by Iannaccone et al1 on the connection between venous plasma endothelin-1 (ET-1) level and retinal vein occlusions (RVO). The authors conclude that elevated ET-1 concentration in the peripheral circulation in their patients may be a systemic marker for retinal vein occlusions. Also, it is conceivable that the elevated ET-1 level they found in the peripheral blood samples could directly promote the development of retinal vascular occlusions (RVOs).

This latter conclusion seems to be unlikely since local retinal vasocostruction 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 concentration 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.2 On the contrary it is probably the open angle glaucoma with elevated intraocular pressure and mild to moderate systemic hypertension that is more frequently associated with RVOs.3 Both of these conditions are characterised by normal ET-1 concentrations.1 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 significant increase in peripheral 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. Was there any difference in the severity of systemic hypertension between hypertensive RVO patients and the uncomplicated hypertensive control subjects? Severe hypertension does influence the systemic ET-1 level. One supposes that all patients were on medication at the time of the blood sampling for ET-1 measurements. Several medicines including antihypertensive drugs and, possibly, β receptor blocker eye drops have an influence on systemic ET-1 levels. Systemic and topical medications should have been compared between the groups in order to rule out their impact on the ET-1 level. It would have been especially interesting and might have supported the authors’ hypothesis on the marker role of venous ET-1 level, if time dependency of the ET-1 level had been investigated individually, at least in the early cases. One may speculate that, early after the development of RVO, systemic ET-1 level may increase, then decrease later till the onset of retinal neovascularisation, which might induce an increase again possibly via an increased expression of vascular endothelial growth factor (VEGF), since VEGF can cause an increased expression of endothelin converting enzyme.4 Interindividual masking the time dependent changes. This may be a reason for the lack of time dependency found by the authors who plotted all individual ET-1 values as a function of time elapsed between the vein occlusion and blood sampling for ET-1 measurement. Finally, I congratulate the authors on their very interesting article.

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Reply

Editor,—We would like to thank Dr Hollo for his interest in our work. He raises a variety of important issues, which give us the opportunity to clarify and expand some points that we raised in the discussion of our paper. First and foremost, we very much agree with him on the very low likelihood of increased plasma endothelin-1 (ET-1) plasma concentrations we observed in our patient population may have pre-existed, or be the cause of, the retinal vascular occlusion (RVO). However, the authors do not provide conclusive evidence to rule out this possibility, which could be addressed only by a large prospective study on ET-1 levels in a population at risk for RVOs, by no means do we support it. In fact, we concluded that the elevated 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, 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, Pourmara and colleagues 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, its 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 interaction 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 were the case, it would contradict the hypothesis that the observed peripheral ET-1 elevations reflected the local retinal event, on which both Dr Höll’s 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), diuretics (n=5), diuretics (n=2), and β blockers (n=1). Although not exactly matched, uncomplicated hypertensives 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 (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 (6.4) pg/ml) or diuretics (15.10 (5.6) pg/ml). 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 Höll’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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Institute of Internal Medicine II, University La Sapienza, Viale del Policlinico 1, 00161 Rome, Italy


OBITUARY

Ronald Francis Lowe
MB, BCh, Mels, MD, FHEA, FRCS(Eng), FRACS, FRACO, FCOPH(UK), FCPh(Meld), 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 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 Unit, Centre for Eye Research Australia, University of Melbourne, The Royal Victorian Eye and Ear Hospital, Melbourne, Australia

NOTICES

Primary Eye Care

The latest issue of the Community Eye Health (no 26) discusses the importance of primary eye care, particularly in the developing world. For further information please contact Community Eye Health, International Centre for Eye Health, Institute of Ophthalmology, 11–43 Bath Street, London EC1V 9EL. Tel: (+44) 171 608 6910; fax: (+44) 171 250 3207; email: eyeresources@uel.ac.uk. Annual subscription £25. Free to workers in developing countries.
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/Esseer course
The 7th Rotterdam International Skull Base Day/Esseer 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 16th Annual Wilmer Institute’s Current Concepts in Ophthalmology will be held on 14–19 March 1999 at the Manor Vail Lodge, Vail, Colorado, USA. Further details: Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Medical Education, Turner 20/720 Rutland Avenue, Baltimore, MD 21205, USA. (Tel: (410) 955-2959; fax: (410) 614-8613; email: cmenet@som.adm.jhu.edu)

Ophthalmological Clinic, 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 für 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 23; email: soc@congrex.se; http://www.congrex.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 in Jerusalem, Israel. 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, Diest Oogheelkunde, de Pintelaan 185, B-9000 Gent, Belgium. Deadline for applications 31 December 1999.
Myopia in diethylstilboestrol exposed amblyopic subjects

PHILIP LEMPERT

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