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 synapses and spines, both in the retina and neurohypophysis.’ High myopia rates in opposite sex twins has been attributed to ocular development in the unusual hormonal environment.3 DES, among various oestrogenic compounds, is the most effective competitive inhibitor for binding oestrogen receptors in the developing monkey brain.4

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 $p = 3.4 \times 10^{-12}$ 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 selective 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.5

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

<table>
<thead>
<tr>
<th></th>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere Cylinder Axis</td>
<td>Sphere Cylinder Axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>Left eye</td>
<td></td>
</tr>
<tr>
<td>7.25 +0.50</td>
<td>85</td>
<td>10.50</td>
</tr>
<tr>
<td>17.75 +1.75</td>
<td>110</td>
<td>10.05</td>
</tr>
<tr>
<td>25.25 +1.00</td>
<td>109</td>
<td>9.50</td>
</tr>
<tr>
<td>19.25 +0.50</td>
<td>95</td>
<td>9.00</td>
</tr>
<tr>
<td>14.75 +1.00</td>
<td>119</td>
<td>8.50</td>
</tr>
<tr>
<td>21.75 +0.50</td>
<td>115</td>
<td>8.00</td>
</tr>
<tr>
<td>18.25 +0.50</td>
<td>105</td>
<td>7.50</td>
</tr>
<tr>
<td>24.75 +1.00</td>
<td>110</td>
<td>7.00</td>
</tr>
<tr>
<td>19.75 +1.00</td>
<td>95</td>
<td>6.50</td>
</tr>
<tr>
<td>26.25 +1.00</td>
<td>115</td>
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<td>23.75 +1.00</td>
<td>109</td>
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</tr>
<tr>
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<td>125</td>
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<tr>
<td>46.25 +1.00</td>
<td>185</td>
<td>1.00</td>
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<tr>
<td>43.75 +1.00</td>
<td>189</td>
<td>0.50</td>
</tr>
<tr>
<td>50.25 +1.00</td>
<td>205</td>
<td>0.00</td>
</tr>
<tr>
<td>47.75 +1.00</td>
<td>209</td>
<td>−0.50</td>
</tr>
<tr>
<td>54.25 +1.00</td>
<td>225</td>
<td>−1.00</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>Amblyopic without DES (n=39)</th>
</tr>
</thead>
</table>
| Spherical equivalent | −14.63 środ | −18.00 | −0.75
| Minimum myopia     | −14.00      | 0.00  | −1.00
| Maximum myopia     | −14.50      | 0.00  | −0.25
| Average             | −1.00       | −0.25 | −0.75
| Standard deviation  | 3.86        | 3.92  | 3.92
| Standard error      | 0.78        | 0.33  | 0.33
| Median              | −5.38       | −1.50 | −1.50

Cataract and season of birth

EDITOR,—Harding and van Heyningen1 have done me the favour of 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 the statistical analysis yielded a significant difference between the season of birth and the prevalence of cataract patients born in the spring on the Indian subcontinent. The control group was age and sex matched to the cataract group. 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, whereas he reported an excess of cataract patients, with some types of cataract, born in the spring on the Indian subcontinent. 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 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 ethically and racially different 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 in 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 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 his 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 anterior subcapsular combination). This confirms the existence of the seasonal effect (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.1

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Osteo-odonto-keratoprosthesis surgery

EDITOR,—We wish to point out some inaccuracies portrayed by the media on osteo-odonto-keratoprosthesis (OOKP) surgery. In 1992, 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 osteo-odontokeratoprosthesis was invented by the late Benedetto Strampelli over 30 years ago.1 A number of surgeons in Britain adopted his technique but their results were disappointing and the technique was abandoned.2

Professor Giuseppe Falcinelli of San Camillo Hospital, Rome, made stepwise improvements on the original technique in the past 20 years, and has been obtaining excellent visual and retention results.3 One of us (CS) was in touch with the San Camillo team by Mr Michael Roper-Hall in 1993 and learnt the technique over the course of the ensuing 3 years. Sergio Pagliarini and Christopher Liu independently surveyed Falcinelli’s results in 1994.4

The “newness” of the operation related only to the introduction of Falcinelli’s OOKP technique into Britain for the first time. We took 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 most of the surgery himself but the television programme had not portrayed him as being the lead surgeon.

Colleagues abroad informed us recently that a certain threshold level. By inducing experimental ischaemic branch RVOs, Pourrainiers and colleagues1 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 suggests 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 were the case, it would contradict the hypothesis that the observed peripheral ET-1 elevations reflected the local retinal event, on which both Dr Hölö 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=3), diuretics (n=2), and β blockers (n=1). Although not exactly matched, 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 Hölö 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).

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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.

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: eyeresource@ucl.ac.uk. Annual subscription £25. Free to workers in developing countries.

OBITUARY

Ronald Francis Lowe, MB,BS(MELD), MD(MELD), 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 service to the Royal Victorian Eye and Ear Hospital and his profession. A tall and imposing man, he also stood tall intellectually and demanded the highest standards of himself and those who worked with him.

Ron首届 trained as a pharmacist before changing to medicine. He graduated in 1939, with first class honours and the prize in surgery. The war years saw him serving in Papua New Guinea and Darwin but towards the end of the war he was seconded to the Royal Victorian Eye and Ear Hospital in Melbourne, where he began his career in ophthalmology. After the war, he became a fellow of the Royal Australasian College of Surgeons and was later promoted to the first fellowship in ophthalmology by the Royal College of Surgeons, England. On his return to Australia and The Royal Victorian Eye and Ear Hospitl he held many senior positions, being a senior ophthalmic surgeon, members of the board of management and ophthalmologist in charge of the glaucoma unit from 1963 to 1975.

He promoted the international standing of Australian ophthalmology, being a foundation professor and vice president of the Academy of Ophthalmological Internationals and in 1998 a foundation member of the Asia–Pacific Academy of Ophthalmology. He has been the only Australian president of this organisation.

Ron published prolifically in many international journals, with his main contributions being in the field of angle closure glaucoma. He produced over 60 papers on this topic and studied anterior chamber geometry, glaucoma screening, and the racial and geographical variation in angle closure glaucoma. His latest writings were of a more historical nature, devoted to chronicling of the development of ophthalmic pioneers, both in Australia and overseas.

I remember sitting with him a few years ago in his austere Melbourne office, several floors above Collins Street, with its rattling trams and 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 closure 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.

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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 4089787; 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 Clinics, 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, Chief 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 DM50 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: ++49-911-393162; 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 5189, S-114 86 Stockholm, Sweden. (Tel: +46 8 459 66 00; fax: +46 8 661 91 23; email: soc@congresx.se; http://www.congresx.se/}

4th Meeting of the European Neuro-Ophtalmology Society
The 4th meeting of the European Neuro-Ophtalmology Society will be held on 29 August–2 September 1999 in Jerusalem, Israel. Further details: Secretariat, 4th Meeting of the European Neuro-Ophtalmology Society, PO Box 90006, Tel Aviv, 61500, Israel. (Tel: 972-3-514000; fax: 972-3-5175674/972-3-5140077; email: euro99@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, Chief 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 Hansens, Dienst 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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