

mechanisms there is no doubt that an important thrombotic mechanism has now been defined.

MUNTHER A KHAMASHTA
Deputy director
GRAHAM R V HUGHES
Director

Lupus Arthritis Research Unit,
Rayne Institute,
St Thomas's Hospital,
London SE1 7EH

- 1 Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *BMJ* 1983;287:1088-9.
- 2 Hughes GRV. The antiphospholipid syndrome: ten years on. *Lancet* 1993;342:341-4.
- 3 Khamashta MA, Hughes GRV. Detection and importance of anticardiolipin antibodies. *J Clin Pathol* 1993;46:104-7.
- 4 Lie JT. Vasculopathy in the antiphospholipid syndrome: thrombosis or vasculitis, or both? *J Rheumatol* 1989;16:713-5.
- 5 Montalban J, Codina A, Ordi J, Vilardell M, Khamashta M, Hughes GRV. Antiphospholipid antibodies in cerebral ischemia. *Stroke* 1991;22:750-3.
- 6 Khamashta MA, Cervera R, Asherson RA, Font J, Gil A, Coltart PJ, et al. Association of antibodies

- against phospholipids with heart valve disease in systemic lupus erythematosus. *Lancet* 1990;335:1541-4.
- 7 Antiphospholipid Antibodies in Stroke Study Group. Clinical and laboratory findings in patients with antiphospholipid antibodies and cerebral ischemia. *Stroke* 1990;21:1268-73.
- 8 Ginsberg JS, Brill-Edwards P, Johnston M, Denburg JA, Andrew M, Burrows RF, et al. Relationship of antiphospholipid antibodies to pregnancy loss in patients with systemic lupus erythematosus: a cross-sectional study. *Blood* 1992;80:975-80.
- 9 Unander AM, Norberg R, Hahn L, Arfors L. Anticardiolipin antibodies and complement in ninety-nine women with habitual abortion. *Am J Obstet Gynecol* 1987;156:114-9.
- 10 Kerslake S, Morton KE, Versi E, Buchanan NMM, Khamashta MA, Baguley E, et al. Early Doppler studies in lupus pregnancy. *Am J Reprod Immunol* 1992;28:172-5.
- 11 McNeil HP, Hunt JE, Krilis SA. Antiphospholipid antibodies—new insights into their specificity and clinical importance. *Scand J Immunol* 1992;36:647-52.
- 12 Bevers EM, Galli M. Co-factors involved in the antiphospholipid syndrome. *Lupus* 1992;1:51-3.
- 13 McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: β_2 I (apolipoprotein H). *Proc Natl Acad Sci USA* 1990;87:4120-4.
- 14 Gharavi AE, Sammaritano LR, Wen J, Elkon KB. Induction of antiphospholipid autoantibodies by immunisation with β_2 glycoprotein 1 (apolipoprotein H). *J Clin Invest* 1992;90:1105-9.
- 15 Elder MG, DeSwiet M, Robertson A, Elder MA, Flloyd E, Hawkins DF. Low-dose aspirin in pregnancy. *Lancet* 1988;i:410.
- 16 Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies. A collaborative randomised trial comparing prednisone with low-dose heparin treatment. *Am J Obstet Gynecol* 1992;166:1318-23.
- 17 Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992;117:303-8.

Electromagnetic fields and childhood cancer

No causal relation has been established

The possibility that exposure to electromagnetic fields causes cancers, including childhood cancers, is one of continuing public concern and scientific debate. The subject has been reviewed on several occasions, most recently and comprehensively by an advisory group set up by Britain's National Radiological Protection Board (NRPB).¹ This group considered four types of exposure: occupational; residential exposure from electrical power lines and domestic wiring (including eight case-control studies of childhood cancer); exposure from electrical appliances (including two case-control studies of childhood cancer); and paternal occupational exposure in relation to cancer in the offspring (six case-control studies—three of central nervous system tumours and three of neuroblastoma).

For the two studies relating to electrical appliances the NRPB group concluded that "these results are incapable of interpretation" (because of the possibility of recall bias and uncertainty about whether the controls were representative). For the studies of parental exposure they concluded that those relating to neuroblastoma did not suggest any relation to parental exposure and that though such a relation might exist in the case of central nervous system tumours, no definite conclusion could be reached.

The eight case-control studies concerned with a possible relation between childhood cancer and residential exposure from power lines and domestic wiring varied greatly in methodology and, particularly, the measure of exposure used: direct measurements of magnetic fields were available for only three of these studies; some based assessments of exposure on classification of electrical wiring configurations. The NRPB group commented that "wire configurations have shown a stronger relationship to childhood cancer than other measures of electromagnetic field exposure."

It suggested that the explanation for this relation might be that these measures provide a better assessment of long term exposure but that, alternatively, types of wiring configuration might be associated with other characteristics of the house concerned and the apparent association with cancer might be an indirect one—that is, might be due to confounding. Jones *et al* have suggested that such an association might arise through selection bias as between cases and controls rather than through confounding.² For these eight case-control

studies the NRPB report concluded that "taken at face value they appear to provide some weak evidence in support of the postulated association, which is less weak for brain cancer than for leukaemia." The advisory group commented on the difficulty of accepting the evidence in view of the problems with selection of control subjects.

Since the NRPB report three further studies of this type have appeared. Two of these, from Denmark (p 891)³ and Finland (p 895)⁴ appear in this issue of the *BMJ* and a third, from Sweden,⁵ has apparently not yet been published in a readily accessible form. (Of the eight earlier studies, seven are listed by Olsen *et al* (their references 1-7) and the eighth appears to be available only as an abstract.⁶)

Do the three new studies give reason to modify the "extreme caution" advocated by the NRPB group in assessing the previous studies? All three studies use calculations of magnetic fields and the two case-control studies use carefully selected controls^{3,5}; the third is a cohort study,⁴ so the problem of control selection does not arise. The two case-control studies show some positive relations between exposure to magnetic fields and the incidence of childhood cancer, though the numbers of exposed cases are small. The findings of the cohort study are essentially negative, particularly when allowance is made for the fact that the one positive finding is partly accounted for by the occurrence of three tumours in a boy with neurofibromatosis.

In the Danish case-control study the strongest effect is found in relation to a grouping of exposure categories chosen after examination of the data, though the analysis is adjusted for this.³ In addition, as the authors point out, it is puzzling that the effect is significant when average exposure for periods of residence close to the power lines is used but not when cumulative dose is used. In the Swedish study⁵ there is some evidence for a relation with childhood leukaemia but no association was found for brain tumours, the type of childhood tumour for which the NRPB group previously found the evidence least weak.

The possibility that magnetic fields associated with electricity transmission may cause some cases of childhood cancer cannot be dismissed, but the lack of consistency among published studies, and the absence of an accepted biological explanation for such a relation, means that we have to

conclude that at present no causal relation has been established. Results from the large case-control studies of childhood cancer currently in progress will be awaited with great interest.

GERALD DRAPER
Director

Childhood Cancer Research Group,
University of Oxford,
Oxford OX2 6HJ

- 1 National Radiological Protection Board. *Report of an advisory group on non-ionising radiation. Electromagnetic fields and the risk of cancer*. Chilton: NRPB. 1992. (Documents of the NRPB. Vol 3 No. 1.)
- 2 Jones TL, Shih CH, Thurston DH, Ware BJ, Cole P. Selection bias from differentiated residential mobility as an explanation for associations of wire codes with childhood cancer. *J Clin Epidemiol* 1993;46:891-5.
- 3 Olsen JH, Nielsen A, Schulgen G. Residence near high voltage facilities and risk of cancer in children. *BMJ* 1993;307:891-5.
- 4 Verkasalo PK, Pukkala E, Hongisto MY, Valjus JE, Järvinen PJ, Heikkilä KV, *et al*. Risk of cancer in Finnish children living close to power lines. *BMJ* 1993;307:895-9.
- 5 Feychting M, Ahlbom A. *Magnetic fields and cancer in people residing near Swedish high voltage power lines*. Stockholm: Karolinska Institutet. 1992. (IMM report 6/92.)
- 6 Lin SR, Lu PY. An epidemiologic study of childhood cancer in relation to residential exposure to electromagnetic fields (abstract). In: Department of the Environment, EPRI. *Contractors' meeting*. Portland, Oregon: DoE/EPRI, 1989.

Free radicals and vascular disease: how much do we know?

They have a role in the function of the normal endothelium and in atherosclerosis

The vascular endothelium is a selectively permeable barrier between the blood and the vessel walls. It is not a passive barrier, however: endothelial cells play an important part in controlling vessel tone, vascular permeability, platelet aggregation, and the adherence of phagocytes such as neutrophils and monocytes. At sites of inflammation neutrophils adhere to the endothelium before entering the inflamed tissue and the endothelial permeability increases. The vascular endothelium can release many products including prostacyclin, adenosine, endothelins, and platelet activating factor.¹

The vascular endothelium also secretes a free radical, nitric oxide (NO[•]), the endothelium derived relaxing factor.² (A free radical, denoted by a superscript dot, is an atom or molecule with one or more unpaired electrons; an unpaired electron is a lone electron in an orbital.) NO[•] inhibits platelet aggregation and adherence of neutrophils and is a powerful vasodilator.² Endothelial cells also generate another radical, superoxide (O₂^{•-}), in vitro.³ Whether endothelial cells release superoxide all the time in vivo, or whether only after an insult (such as ischaemia and reperfusion) is unknown.

When two free radicals meet they can join their unpaired electrons and form a non-radical. Superoxide and NO[•] react quickly to form ONOO⁻.⁴ As a result, superoxide antagonises the vasodilatory action of NO[•] and adding superoxide dismutase (an enzyme that scavenges superoxide) prolongs the life of NO[•]. Indeed, it has been suggested that vascular over-production of superoxide might be one cause of hypertension.⁵ A further suggestion is that the ONOO⁻ (peroxynitrite) produced by the reaction between superoxide and NO[•] is itself cytotoxic.⁶ Hence, the generation of superoxide by vascular endothelium and its interaction with NO[•] both warrant further investigation.

Endothelial cells can be killed by high concentrations of hydrogen peroxide by mechanisms that involve damage to DNA and proteins caused by free radicals as well as an increased concentration of intracellular free calcium ions.^{7,8} Low concentrations of hydrogen peroxide are, however, efficiently dealt with by catalase and glutathione peroxidase, enzymes that metabolise hydrogen peroxide in the endothelium.⁹ Indeed, sublethal exposure of endothelium to hydrogen peroxide (for example, produced by neutrophils adhering to endothelium) might contribute to the increases in vascular permeability, the synthesis of platelet activating factor and tissue plasminogen activator, and the adhesion of more neutrophils to the endothelium.¹⁰

Endothelial cells can also be injured by high concentrations of organic peroxides, such as the lipid peroxides produced when free radicals attack polyunsaturated fatty acid side chains and cholesterol in membranes and lipoproteins.

Fortunately, the lipid peroxide concentration in plasma from healthy humans is submicromolar.¹¹ Concentrations are, however, higher in hyperlipidaemic patients, even during treatment with lipid lowering drugs, although whether concentrations are high enough to injure the endothelium is unknown.

Injury to endothelium by chemical or mechanical means or by infection with certain viruses may lead to atherosclerosis.^{12,13} Evidence is accumulating that reactions involving free radicals, especially peroxidation of low density lipoproteins in vessel walls, are major contributors to the development of atherosclerosis.¹³ Thus low density lipoprotein in the early stages of peroxidation promotes adherence of monocytes to endothelium.¹⁴ Monocytes develop into macrophages within the vessel wall: both cell types can generate superoxide and hydrogen peroxide, and macrophages may also generate NO[•]. Extensively peroxidised low density lipoprotein can be taken up by macrophages to form "foam cells" laden with lipid, which are present even in early atherosclerotic lesions.¹² Smoking aggravates atherosclerosis and imposes a powerful stress due to free radicals on the human body.¹⁵ An adequate dietary intake of vitamin E seems protective against vascular disease, perhaps because vitamin E inhibits peroxidation of lipids.¹³ How much is adequate is another unanswered question; despite recent enthusiasm for dietary supplementation with "antioxidant" nutrients (such as vitamins E and C and the carotenoids) we do not know what dietary intakes are optimal.

In the early days of research into free radicals scientists concentrated on their damaging effects. Indeed, they are damaging in excess (even too much NO[•] is cytotoxic, destroying mitochondrial iron-sulphur proteins). But now we know that free radicals are often useful in small amounts—for example, as important agents killing foreign organisms ingested by phagocytes and as mediators of some of the effects of acute inflammation.^{10,12,14} An important clinical question is the extent to which antioxidants could prevent or treat the devastating effects of advanced atherosclerosis.^{12,13,16}

BARRY HALLIWELL
Professor of medical biochemistry

Pharmacology Group, King's College,
University of London,
London SW3 6LX

- 1 Lefer AM, Lefer DJ. Pharmacology of the endothelium in ischemia-reperfusion and circulatory shock. *Ann Rev Pharmacol Toxicol* 1993;33:71-90.
- 2 Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacol Rev* 1991;43:109-42.
- 3 Arroyo CM, Carmichael AJ, Bouscarel B, Liang JH, Weglicki WB. Endothelial cells as a source of oxygen free radicals: an ESR study. *Free Radical Research Communications* 1990;9:287-96.
- 4 Huie RE, Padmaja S. The reaction of NO with superoxide. *Free Radical Research Communications* 1993;18:195-9.
- 5 Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Does superoxide underlie the pathogenesis of hypertension? *Proc Natl Acad Sci USA* 1991;88:10045-8.