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Dietary selenium: time to act

Low bioavailability in Britain and Europe could be contributing to cancers, cardiovascular disease, and subfertility

The essential trace element, selenium, which we largely obtain from bread and cereals, fish, poultry, and meat, plays a vital part in many metabolic functions. While new research increasingly suggests its relevance to disease prevention, evidence that dietary intake is falling in some parts of the world is giving cause for concern.

Selenium is a key component of a number of functional selenoproteins required for normal health. The best known of these are the antioxidant glutathione peroxidase enzymes, which remove hydrogen peroxide and damaging lipid and phospholipid hydroperoxides generated in vivo by free radicals and other oxygen derived species. If not removed, lipid hydroperoxides impair membrane structure and function[1] and cause blood clotting disturbances by decreasing the production of prostacyclin while increasing the production of thromboxane.[2] Furthermore, lipid hydroperoxides are not stable end products but, in the presence of transition metal ions, can decompose to give further reactive free radicals and cytotoxic aldehydes.[3] Such secondary products may initiate more lipid peroxidation, promote atherosclerosis, damage DNA, and metabolically activate carcinogens.[3]

Selenium also plays an important role in the control of thyroid hormone metabolism. The iodothyronine deiodinases, which are responsible for the conversion of thyroxine (T4) to its active form, triiodothyronine (T3), are selenoenzymes.[4] Selenium deficiency may cause reduced growth rates owing to a feedback response which lowers triiodothyronine mediated synthesis of growth hormone in the pituitary,[5] while a combined deficiency of selenium and iodine exacerbates hypothyroidism.[4]

Selenium is important for proper reproductive performance. Sperm capsule selenoprotein is a structural selenoprotein found in the midpiece region of the sperm tail.[6] In selenium deficiency, morphological anomalies in this region give rise to spermatozoa with impaired motility.[7] Selenium is also needed for normal testosterone metabolism and testicular morphology, which may explain the presence of several other selenoproteins in the male gonads.[7]

The activity of these selenoproteins, and of others with as yet unidentified functions, depends on adequate selenium supply from the diet. Selenium enters the food chain through plants. Dietary intakes show a large geographical variation, mainly because of differences in selenium bioavailability, which is generally low in Europe. Areas of China where the soil is extremely low in selenium are associated with clear selenium deficiency diseases—an endemic cardiomyopathy (Keshan disease) and a deforming arthritis (Kashin-Beck disease).[8] Less overt selenium deficiency has been shown in several studies to have adverse effects on susceptibility to many other disorders, including cardiovascular disease and cancers.[3 8 9]

Evidence is accumulating that European intakes of selenium are falling. Some 22 years ago, selenium intakes in Britain were 60 μg/day,[10] not high when compared with American intakes but very much higher than the 34 μg/day found in a survey undertaken for Britain's Ministry of Agriculture, Fisheries, and Foods in 1994[11] and at least approaching the British government's own defined reference nutrient intake of 75 μg/day for men and 60 μg/day for women. (The ministry has since commissioned further studies.)

Intakes and blood levels falling

This substantial fall in selenium intake can largely be explained by the drop in imports of selenium rich, high protein wheat for breadmaking flour from North America. Levies imposed on foreign imports when Britain joined the European Union, coupled with changes in breadmaking technology, have resulted in increased use of low selenium, lower protein European and British varieties. Parallel reductions in intake have occurred in other European Union countries for similar reasons; added to which, bioavailability of selenium may have fallen in areas subject to acid rain or excessive artificial fertilisation of soils, both of which reduce plant absorption of the mineral.

These falling intakes are reflected in diminishing serum and whole blood selenium concentrations[12-15] (see figure 1). In a more recent British study, my colleagues and I found low mean serum selenium (50.8 (SD 17.3) μg/l) in third trimester healthy pregnant women in Oxford.[2] Similarly low values (47 (13) μg/l) were found in healthy Northern Irish pregnant women at delivery.[16] While third trimester pregnancy accounts for an average fall of 28% in selenium concentrations (mean of nine European studies), these levels are nonetheless towards the lower end of a range of 21 world values measured at this stage in pregnancy (28-190 μg/l).

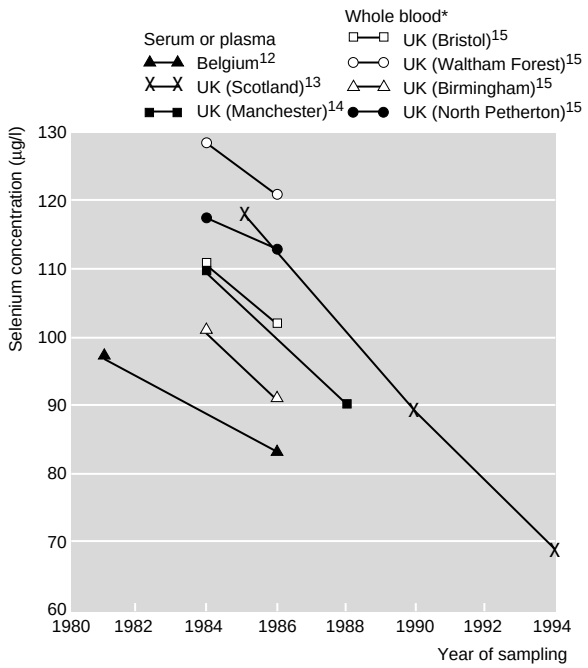

Fig 1 Decline in serum, plasma, or whole blood selenium concentrations with time. Whole blood concentrations are normally 10-25% higher than serum or plasma values; *measurements were made on same subjects in both years

From a review of studies published between 1983 and 1993,[12] a mean value for serum selenium in seven European Union countries can be calculated as 79 µg/l, again towards the bottom of the range of study values (50-197 µg/l). Serum selenium values of 100 µg/l are believed to be required for optimal activity of cytosolic glutathione peroxidase,[17] an indicator of selenium repletion. Current values seem likely to be considerably below this threshold.

This reduced selenium status gives further cause for concern in the light of some new information. Beck and colleagues have shown that relatively harmless viruses can become virulent by passing through a selenium deficient host.[18] This has been mooted as an explanation for the first appearance of HIV in Zaire, a country with a selenium deficient population, and for the appearance of new strains of influenza virus in China.[18] A recent British study showed a significantly higher risk ($P<0.005$) of spontaneous abortions in women with low concentrations of serum selenium.[19] Sperm motility improved from 17.5% to 35.1% ($P<0.01$) in subfertile men supplemented with selenium in a controlled double blind trial.[20] A recently completed study, which randomised 1312 patients to receive placebo or 200 µg of selenium a day, showed a 50% lower cancer mortality ($P<0.002$) in those receiving selenium.[9]

Is it not time to consider addressing the problem of low selenium intakes? In Britain virtually all farm animals get mineral supplements which have included selenium since 1978, when its efficacy in preventing animal disease was accepted. Should we humans be lagging so far behind? Perhaps it is time to consider measures such as those adopted in Finland, another country with low soil selenium, which has been adding sodium selenate to its fertilisers since 1984. Alternatively, addition of selenium to bread flour along with the statutory mineral additives of calcium and iron may be a possibility. In the meantime, judicious use of supplements (staying well below the toxic level of 800 µg/day) or a daily helping of Brazil nuts, the richest natural source of selenium, would seem our best option.

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Introducing the postoperative care team

Additional support, expertise, and equipment for general postoperative inpatients

The 1992-3 and 1993-4 national confidential enquiries into perioperative deaths[1 2] record the use of monitoring, the availability of facilities, and the experience of the doctors caring for patients. About two thirds of patients died three or more days after surgery, with most of the deaths taking place on a ward. A high percentage of those who died had had a cardiac or respiratory complication, renal failure, or infection, and some of these complications might have been preventable.

Preoperative preparation and a high standard of anaesthetic care are essential, as they affect postoperative events.[3 4] By the end of surgery it may be too late to substantially alter outcome for some patients.[5] On the other hand, aggressive postoperative optimisation of physiological values has been shown to decrease mortality and morbidity in selected groups of patients.[6 7] The principle of proactive treatment to prevent complications could be widened to a larger group of postoperative patients.

In the postoperative period, vital organ function may be at risk because of inadequate perfusion and oxygen delivery. Breathing may be limited because of pain or oversedation, contributing to chest infection or episodes of hypoxaemia.[8] Cardiac ischaemia may result from hypertension, tachycardia, or hypoxaemia.[9] Deep vein thrombosis may be more likely with poor analgesia limiting early mobilisation and inadequate fluid replacement contributing to venous stasis. The incidence of wound infection and bowel anastomotic breakdown are likely to be related, in part, to postoperative factors. Many of these adverse events do not manifest for several days after surgery.

In high risk patients physiological values should be optimised before surgery, and it should be possible to lay down targets to be achieved in the postoperative period. These would certainly include an oxygen saturation of greater than 90%; the absence of episodes of significant depression of ST segment on electrocardiograms; adequate and appropriate cardiac output, renal output, and fluid replacement; excellent analgesia; and the absence of oversedation. Techniques exist for appropriate monitoring and management.

It is possible to imagine a ward where effective analgesia is available to all patients after surgery, and fluid management is guided by established critical care techniques. Pulmonary exercises may decrease the incidence of respiratory complications. Oxygen therapy is effective at preventing hypoxaemia[10] and would be titrated against oxygen saturation as measured by pulse oximetry. Continuous electrocardiographic monitoring, with computer assisted processing to detect abnormalities, would provide early warning of dysrhythmias and ischaemia. Appropriate early nutrition would be encouraged and measures taken to minimise the risk of infection. Informed medical advice would be readily available to guide management. All of the above should be available on a routine surgical ward, but experience suggests that this is rarely the case.

The confidential enquiries rightly identify a "substantial shortfall in critical services," and a high dependency unit should fulfil all of the functions described above. Although not as costly as an intensive care unit, the high dependency unit is none the less an expensive option that is unlikely to be available to most postoperative inpatients, particularly beyond the first few hours after surgery. Acute pain care teams have evolved to look after the analgesia needs of postoperative patients.[11] It may be time to widen the concept to form a postoperative care team. Regular postoperative care rounds and a team of postoperative care nurses should be able to support nursing and medical staff on the surgical ward and provide additional expertise and equipment to assist in the care of most postoperative inpatients. The concept of early recognition and intervention may also be applicable to selected medical patients, such as those at risk of having a cardiac arrest.[12]

It remains to be proved whether a comprehensive system of continuing postoperative care would decrease morbidity and mortality, provide greater comfort and satisfaction, or allow patients to be safely discharged at an earlier time than is routine at present. If improvements in outcome after anaesthesia and surgery are to continue it may be necessary to take on the challenge of postoperative care.

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Erasing the global divide in health research

Collaboration provides answers relevant to developing and developed countries

Developing and developed countries are often viewed separately with respect to their health problems, health systems, and health services research. So although more than 90% of the world's "potential years of life lost" belong to the developing world, only 5% of global research funds are devoted to studying the developing world's health problems.[1] Chronic diseases such as cancer, heart disease, and mental illness are usually regarded as problems of the developed world, but, as people live longer, developing nations will need strategies to cope with the associated health burden. Morbidity and mortality from communicable diseases are largely problems of the developing world but there are notable exceptions, in particular HIV infection. And for many healthcare problems the solutions are the same, irrespective of the developmental stage of the country.

When deciding whether to implement a specific healthcare intervention, in whatever setting, there are certain basic steps that should be taken. These include: appraising local needs and health priorities, evaluating the strength and generalisability of the evidence, and estimating the likely cost-benefit ratio to both the health service and the community. In addition, interventions based on research in developed countries should be put to two further tests by health service planners in developing countries: firstly, an assessment of the feasibility of introducing the intervention within the existing health service, and, secondly, an assessment of its cultural sensitivity. Studies must be relevant to the population in which they are carried out.[2]

A systematic review of the effect of family intervention strategies for patients with schizophrenia showed that such interventions reduced the relapse rate in patients from Europe, North America, and China.[3] However, there were striking variations in the emotional responses and styles of coping adopted by relatives in different countries.[4] Use of a standardised intervention across cultures may not always be appropriate. Microethnographic techniques can be used to develop interventions that are more culturally orientated.[5]

High quality collaborative research conducted in developing countries can provide evidence of relevance and value to the developed world. Many health conditions, such as eclampsia and neurocysticercosis, occur so rarely in developed countries that clinical trials could never be conducted there. In such instances advances in our understanding of the treatment of these conditions are likely to come from developing countries. For example, the use of anticonvulsants in the management of eclampsia has been the subject of controversy for over 70 years, but a recent randomised trial conducted in South America, Africa, and India (though largely coordinated from Britain) demonstrated that magnesium sulphate was the drug of choice.[6] The results of this trial have been widely accepted by the international obstetric community; for example, the Royal College of Obstetricians and Gynaecologists (London) is currently incorporating this evidence into its practice guidelines.

There are many advantages to conducting research in developing countries: the availability of patients, the existence of well trained investigators, the lower costs, and the benefit to health systems and other institutions from financial investment. Many trials of international relevance could be effectively carried out in developing countries. Indeed, the number of international publications on health research from developing countries has increased steadily over the past two decades.[7]

From the examples cited above, it is clear that the future of health services research lies in international collaboration. Aggregating results of well conducted randomised clinical trials from developing and developed countries is both desirable and practical, as has been clearly shown by the work of the Cochrane Collaboration.[3 8] People from developing countries are currently producing Cochrane reviews; some are using these as the essential starting point for their own high quality primary research. Such multinational collaboration is the surest way to answer questions of global relevance.

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Epilepsy: a progressive disease?

Still no answer to the controversy over whether seizures beget more seizures

See p 401

It is amazing how after years of scientific research and therapeutic progress many simple and basic questions about the epilepsies remain unanswered. Even the natural course of epilepsy is not well known because of the widespread use of antiepileptic drugs. Gowers suspected that seizures trigger subsequent seizures or, in other words, that there is a facilitation phenomenon.[1] This idea still survives but has yet to be substantiated. We also do not know if antiepileptic drugs alter the natural course of epilepsy and prevent chronicity and intractability developing. Are the risks of further seizures in newly diagnosed patients (especially children) worth the side effects associated with antiepileptic drugs? What is the optimum time to begin treatment? Clinical studies have produced diverging and sometimes conflicting views on these problems.

In this week's *BMJ*, van Donselaar *et al* (p 401) followed 204 untreated children aged 1 month to 16 years who experienced one (123 patients) or more idiopathic or "remote symptomatic" tonic-clonic seizures (including seizures with partial onset).[2] They analysed the time between seizures until the start of treatment, the fourth untreated seizure, or the end of the two year follow up. Only a few patients showed an accelerating pattern with decreasing time between seizures. Most showed a varying or slowing pattern.

These results contrast with those of Elwes *et al* in 1988.[3] In a retrospective, hospital based study, they examined the time between primary or secondary generalised tonic-clonic seizures in untreated patients. Many of them had an accelerating seizure pattern in the early stages of the disease. Even if their population of patients is not comparable with that studied by van Donselaar *et al*, their findings are in keeping with the observation that remission rates with antiepileptic drugs seem inversely correlated with the number of seizures before treatment.[4,5] This implies that early treatment may be important to prevent epilepsy from evolving into a chronic and more intractable state.

The concept of evolving epileptogenesis has been fuelled by studies on the "kindling" model of epilepsy. The term kindling refers to a dynamic phenomenon whereby repeated administration of an initially subconvulsive electrical stimulus results in progressive intensification of seizure activity culminating in a generalised seizure.[6] This increased sensitivity to the stimulus (and the reduction of seizure threshold) is permanent. Kindling can be established in numerous mammalian species by electrical stimulus and various pharmacological agents, including excitatory amino acids like kainic acid. However, kindled animals rarely develop either spontaneous seizures or the brain lesions observed in human epilepsy.

Whether similar mechanisms operate in the development of epilepsy in humans has not been established, but there are certainly valid arguments to suggest that this may be the case. Adults with complex partial epilepsy arising from one temporal lobe may progress so that both temporal lobes eventually trigger complex partial seizures. In a series of patients with temporal brain tumours, Morell has quite convincingly shown that secondary epileptogenesis takes place in humans, leading to the development of mirror foci.[7] Furthermore, he provided evidence that the likelihood of a secondary focus becoming permanent rises with increasing frequency of seizures, which again underscores the importance of rigorous seizure control. In a retrospective and longitudinal study of a large number of electroencephalograms, Hughes found that the incidence of bilateral foci, as opposed to unilateral foci, increased with age at a rate of almost 1% a year.[8] Clinical signs of the development of bilateral temporal foci were seen in 34% of patients. The frequent occurrence of multiple foci, usually in synaptically connected sites, in the temporal lobes of patients with epilepsy also raises the possibility of kindling-like phenomena in humans.[9]

However, the situation is not as clear as it may seem. Van Donselaar *et al*'s study is not the only one that does not support the notion that repeated seizures aggravate the epileptic process. Epidemiological surveys have been conducted in developing countries where epileptic patients remain untreated for years after the onset of seizures. The prospect of achieving remission spontaneously[10] or after treatment, even in patients with prolonged epilepsy, remains high.[11] In industrialised countries also untreated epilepsy may run a benign course in some patients.[12] Community based studies suggest that in most patients the long term prospect of seizure control is good and that the remission rate improves with increasing duration of follow up.[13]

Epilepsy is certainly not a homogeneous disease, and the work of van Donselaar *et al* suffers from patient and seizure heterogeneity, which is a serious shortcoming. The clinical diversity of the epilepsies implies a diversity of aetiologies and cellular mechanisms. A primary generalised tonic-clonic seizure in a baby may have little in common with a secondary generalised seizure in a 16 year old. Their results are certainly not applicable to other types of epilepsies such as primary generalised absence, juvenile myoclonic epilepsies, or benign rolandic epilepsy, which carry a different prognosis.

Van Donselaar *et al*'s study is therefore another piece of the puzzle but it does not provide a definitive answer to the old controversy: "Do seizures beget seizures?" The question is important because the answer would influence our treatment strategy after a first seizure. Further prospective studies on larger groups of more homogeneous patients are needed, and factors that contribute to the development of seizure chronicity and intractability should be identified. For the time being, it remains reasonable to delay treatment until after a second or third seizure, unless clinical features such as more than one seizure type or a neurological deficit augur poor seizure control.[5]

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Children in cars

Child restraints should be built in safety features, not optional extras

Cars are not designed with children in mind. There can be little dispute about that. This will be obvious to any parent obliged to purchase the procession of products necessary for the safe transportation of children. Although children make up nearly 20% of the population, the car industry has yet to design and build cars that afford the same degree of crash protection for children as for adults without the need to buy and install additional safety equipment.

The issue is not trivial. In 1995 in England and Wales there were 73 child passenger deaths and 1073 serious injuries. The death rate per passenger mile has fallen, but this has been offset by large increases in car travel.[1] Between 1985 and 1994, the number of car miles travelled by children increased by 40%, from 2260 to 3160 miles per person per year.[2] With children spending more and more time in the car, the safety of child occupants is increasingly important.

Airbags are nitrogen filled buffers, concealed within the dashboard and steering wheel, that inflate in a crash, preventing potentially fatal injuries to the occupant's head and chest.[3] Air bags save lives, but, with their introduction, the safe transportation of children has become even more of a nightmare. A flurry of case reports has raised concern about the use of rear facing child restraints in the front seat of cars fitted with airbags. In a crash, an infant in a rear facing restraint could be killed or seriously injured when the explosive force of the airbag impacts on the back of the restraint.[4]

The Society of Motor Manufacturers and Traders has responded with an education campaign urging parents "not to fit a rear facing child restraint in a seat protected by an airbag." In addition, every car with an airbag on the passenger side is to be fitted with a warning pictogram. It is reassuring that the car industry is taking steps to warn parents, but, as campaigns go, this one does not score highly. Firstly, user testing has shown that the pictogram is poorly understood. Secondly, the campaign poster shows a toddler in a forward facing restraint in the back of a car, an odd choice bearing in mind that the problem concerns infants in rear facing restraints.

It is recommended that infants use a rear facing restraint until they weigh 9 kg or are 1 year old. So, if a car has a passenger side airbag what should parents do? Fortunately, advice from the Department of Transport is clearer: infants should travel facing rearward in the back of the car. Sound advice perhaps, but it will not receive a warm welcome. Many parents understandably do not like placing infants facing rearward on the back seat. There is, however, a technical fix on the horizon. A "smart air bag" is being developed that deactivates in the presence of a child restraint. In the meantime parents need advice on how to transport infants in cars with airbags. The message should be short and simple, outlining what to do rather than what to avoid.

The safe restraint of children could be as easy as it is for adults. But the car industry likes to make a profit, and safety and profit are sometimes in conflict. For example, the concept of the airbag was first mooted in the 1940s, but half a century later only a third of new cars have airbags. Despite well documented safety benefits, the introduction of airbags was vigorously opposed by Chrysler chairman Lee Iacocca, Henry Ford II, Richard Nixon, and Ronald Reagan. They feared increased production costs would reduce profits and competitiveness. The delay may have led to thousands of unnecessary deaths in road traffic accidents.[5 6] Child restraints, like airbags, should be built in safety features, not optional extras. If children must be condemned to motorised monotony then cars should be designed with them in mind.

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