The importance of mass screening for neuroblastoma has long been controversial. Many investigators have confirmed that tumours found on screening differ from those found clinically in several biological and clinical features. Moreover, studies have given conflicting results on whether screening decreases the incidence of tumours with poor prognostic features at older ages. Japan is unique in having a national neuroblastoma screening programme. More than 80% of Japanese infants are screened for this tumour.

Comparison of a population being offered a screening programme with one not having such a programme would be a useful means of resolving whether mass screening is worthwhile. In today's Lancet Wood and coworkers report their comparison of standardised incidence ratios (SIRs) for neuroblastoma in the province of Quebec and in two control populations derived from the United States Surveillance, Epidemiology and End Results data. SIRs in Quebec were 2·17, 2·85, and 1·42 for the whole group, for infants, and for children aged 1–6 years, respectively. The two control groups did not significantly differ from each other in these SIRs. However, SIRs for older age groups in two control groups were not significantly different from SIR for older age groups in Quebec. This result is almost equivalent to those of Yamamoto and coworkers and my findings.

One important result shown in the paper by Wood and coworkers is that the screening programme failed to reduce the incidence of unfavorable advanced stage disease in older age groups. Although one Japanese study has shown that screening led to some decrease in incidence at the age of 3 years, the finding implies that the tumours detected by screening would, if not picked up on screening, have grown very slowly over 3 years—ie, they are not rapidly progressing tumours. By contrast, many tumours found clinically in children who had screened negative at 6 months of age have poor prognostic features. Experience in Miyagi Prefecture, Japan, showed that 18 children who had screened negative but later developed tumours at the median age of 2 years (range 1–7 years), three had stage III disease and 12 had stage IV disease. Furthermore, only three of the 18 children had tumours without unfavourable histological features or amplified N-myc genes, and six of 12 tumours whose N-myc amplification was examined showed amplified N-myc genes (more than seven copies). These findings are similar to those obtained by Kaneko and coworkers, and they indicate that screening is not effective in detecting aggressive tumours at the asymptomatic stage. The nature of the tumours detected on screening has prompted an attempt at conservative treatment for carefully selected patients—ie, follow-up with imaging studies and measurements of urine catecholamine metabolites and other tumour markers instead of surgical resection of tumours. At least 21 children, 20 with stage I, II, or IV-S and one with stage III, have been followed up for 2 to 32 months. In most children there has been a gradual decline in the level of tumour markers and tumour size. Those in whom tumour size increased a gradual decline in the level of tumour markers and tumour size. Those in whom tumour size increased prompted an attempt at conservative treatment for carefully selected patients was acceptable but still experimental and it was not recommended for routine use. Conservative treatment is very stressful both for the families and health staff because there is no way of distinguishing those tumours that carry a poor prognosis from spontaneously regressing ones. Legal repercussions can also be expected. This stressful effort at conservative management may help extend knowledge or confirm what is known about the nature of neuroblastomas detected on screening, but it is unlikely to give us the further information required for decision making. The conservative approach may be the best choice to prevent harm to young children in the prevailing situation, but calling a halt to the national screening programme is a better option.

Fumio Bessho
Department of Paediatrics, University of Tokyo Hospital, Tokyo 113, Japan


Electrical stimulation techniques
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An article in today's Lancet and another in the journal recently on electrical spinal cord stimulation (ESCS) indicate that this may be an effective treatment in conditions as diverse as painful diabetic peripheral neuropathy and refractory urge incontinence. Tesfaye and colleagues report that in eight out of 10 patients ESCS relieved chronic diabetic neuropathic pain and improved quality of life. The two patients not responding to treatment had complete absence of vibration and joint position sense, which indicated large-diameter afferent and/or dorsal-column damage. These two non-responses are not surprising since ESCS evolved as a clinical application of Mitzack and Wall's gate-control theory, the pain-alleviating effect being based on activity in intact large-diameter afferents. Initially ESCS, as well as other forms of electrical stimulation—including high-frequency transcutaneous electrical nerve stimulation, which aims at the activation of large diameter afferents or their central projections—were widely and uncritically applied to practically all...
kinds of pain. As a result, the long-term effects were poor and these methods fell into disrepute. With the growing knowledge that adequate management of pain requires that different types of pain be carefully identified and analysed, the pain conditions most likely to respond to electrical stimulation could be identified. It is generally agreed that electrical stimulation is effective in neurogenic forms of pain. There is no convincing evidence that endogenous opioids or monoamines are involved in the pain-relieving effects of high-frequency sensory stimulation. Experiments indicate that electrical stimulation is followed by a decrease in the excitatory aminoacids glutamate and aspartate in the dorsal horn, and that this effect is mediated by a GABAergic mechanism. A central role of GABA in the effects of electrical stimulation is supported by the finding that the ES-induced inhibition of nociceptive neurons at the spinal cord level could be counteracted by a GABA antagonist. Supraspinal mechanisms activated via spinobulbar, spinothalamic, and spinothalamo cortical connections and their respective descending-pain-controlling pathways have been implicated.

Tefsaye and colleagues also report that the patients obtaining pain relief with ESCS had improved exercise tolerance, which suggests that it induces circulatory changes. This suggestion is supported by studies showing that electrical stimulation may counteract peripheral tissue ischaemia and increase healing of diabetic ulcers. The reversal of tissue ischaemia and increased tissue healing may be attributed to other mechanisms than those involved in the relief of neurogenic pain. It may be suggested that these effects are due to antidromic stimulation of afferent nerves resulting in the release of vasoactive substances in the periphery such as calcitonin gene-related peptide. Furthermore, supraspinal and spinal cord mechanisms, resulting in an inhibition of the sympathetic tone, are likely to be involved.

In the study by Bosch and Groen, afferent stimulation was used in yet another context. Bosch and Groen reported that electrical stimulation applied to the S3 sacral spinal afferent nerves in four multiple sclerosis patients with refractory urge urinary incontinence resulted in a decrease in the number of leakage periods by 4 to 0-3 per 24 h. The hyperreflexia disappeared in one, improved in two, and got worse in one, perhaps because of clinical progression of the multiple sclerosis. The results may be attributed to stimulation of pudendal nerve and limb-muscle afferents, resulting in activation of supraspinal and spinal inhibitory mechanisms interrupting detrusor contractions.

The numbers of patients investigated in the two Lancet studies are small. However, the investigations have been meticulously carried out and point to significant clinical effects in patients in whom no other obvious treatment strategy is applicable and the researchers themselves conclude that further studies are needed. The development of strict indications and the refinement of electrical stimulation, with the development of methods improving its efficacy, have been hindered by poor knowledge about the mechanisms underlying its effects. What is needed now is closer cooperation between basic scientist and clinician. Electrical stimulation techniques do merit further consideration especially since these techniques utilise endogenous mechanisms and do not carry the risks of surgery or drug side-effects.

**Thomas Lundeberg**

Department of Physiology and Pharmacology, Department of Medical Rehabilitation, Karolinska Institutet, Stockholm, Sweden


**Cardiovascular disease in patients with chronic renal failure**

The increased availability of dialysis and renal transplantation has unmasked the clinical importance of co-morbid conditions associated with kidney disease. At the recent American Society of Nephrology meeting (New Orleans, Nov 3–6) a symposium organised jointly with the American Heart Association outlined recent developments in our understanding of factors that contribute to atherosclerosis in patients with chronic renal failure. Concerns that such individuals are at high risk of cardiovascular disorders, first voiced over 20 years ago, have proved justified. Data from the Registry of the European Dialysis and Transplant Association confirm that patients receiving renal-replacement therapy experience a 16-fold to 19-fold increased risk of myocardial ischaemia and infarction when compared with age-matched and sex-matched populations without renal failure. Younger patients and those with diabetic nephropathy are at especially high risk. Cardiac failure is also commonly seen in association with renal disease, and cardiovascular causes now collectively account for approximately 50% of deaths among those who would have naturally succumbed to uraemia.

Efforts to extend the life-expectancy of patients with chronic renal failure may therefore depend as much on the appropriate management of cardiovascular disease as on improving dialysis techniques or prolonging the survival of transplanted kidneys. Although concerns that the dialysis process itself may accelerate atherosclerosis have proved largely unfounded, many well-recognised cardiovascular risk factors may be present in individuals who require renal-replacement therapy. Hypertension occurs early in the course of renal disease and is present in 75–80% of patients who reach "end stage". Left-ventricular hypertrophy can be found in over 50% of dialysis patients and probably results from a combination of hypertension and anaemia. In 50–75% of dialysis patients hypertriglyceridaemia with depressed high-density lipoprotein levels complicates renal impairment, whilst 50–80% of renal transplant recipients develop hypercholesterolaemia.

Delegates at the conference heard that endothelial dysfunction, increased oxidant stress, and raised plasma homocysteine levels can be added to the list of risk factors that may contribute to vascular injury in patients with chronic renal failure. Uraemia may modify the vascular...