

## Lead and motor neurone disease

The term "motor neurone disease" describes a progressive degenerative disorder of the central nervous system affecting the motor nuclei of the cranial nerves, the anterior horn cells of the spinal cord, and the descending corticospinal (pyramidal) tracts. This is the definition of the term as used in Britain, and when the initial brunt of the disease falls on the brain stem it usually produces progressive bulbar palsy, and when predominantly the spinal anterior horn cells are initially affected progressive muscular atrophy. The term "amyotrophic lateral sclerosis" is generally used when the early symptoms and signs are due to damage to the corticospinal tracts and when there is comparatively little evidence of lower motor neurone degeneration. In the United States, on the other hand, this term is often used (as is "motor system disease") as if it were synonymous with the British motor neurone disease.

Motor neurone disease is generally sporadic, rarely familial, and occurs worldwide and in all races. Symptoms usually develop between the ages of 50 and 70 years. The incidence is about 1 new case per 100 000 population per year, with a prevalence of 2.5-7 per 100 000.<sup>1,2</sup> The disease is, however, endemic in the Chamorro people on the island of Guam, where it shows a high familial incidence, often occurring in association with the so-called Parkinsonism-dementia complex. Nevertheless, it is still uncertain whether this form is genetically determined or whether it is due to a combination of genetic and environmental influences.<sup>3-6</sup>

Both the aetiology and pathogenesis of the condition remain obscure. While it may sometimes follow many years after an attack of acute anterior poliomyelitis<sup>7</sup> or encephalitis lethargica,<sup>8</sup> no concrete evidence favours viral infection, and attempts to isolate a causal virus from the spinal cords of patients have been unsuccessful.<sup>9,10</sup> A link with malignant disease has been postulated,<sup>11</sup> but recent work suggests that this is a chance association.<sup>12</sup> Other unsubstantiated associations that have been suggested have been with diffuse angiopathy,<sup>13,14</sup> disorders of lipid and carbohydrate metabolism,<sup>15,16</sup> high concentrations of manganese and calcium in the central nervous system,<sup>17</sup> and exocrine pancreatic dysfunction. There is some evidence<sup>18</sup> of disordered protein metabolism in neurones (but not in myelin) and of abnormal DNA-directed mRNA synthesis in anterior horn cells,<sup>19</sup> but whether these abnormalities indicate a fundamental pathogenetic mechanism is still uncertain. The postulate that the condition is due to premature aging in motor neurones, showing some indirect affinity with the process which occurs in cortical neurones in the presenile dementias, is commonly advanced but remains unsupported.

In 1970 Campbell and colleagues<sup>20</sup> suggested that chronic lead intoxication might be an important factor, but this view was not widely accepted. Nevertheless, Conradi and colleagues<sup>21</sup> found raised lead concentrations in the cerebrospinal fluid of patients when compared with controls, and more recently<sup>22</sup> they have reported raised plasma lead concentrations in 16 patients compared with 18 control subjects. The plasma concentrations found, by the technique of flameless atomic absorption spectrophotometry, were lower in both the patients and the controls than those reported earlier for normal individuals; but nevertheless the concentrations in the patients were significantly higher than in the controls. They postulate that the exposure of the motor end plates to increased amounts of circulating lead in the plasma may result in the uptake of lead by the motor neurones and that this may be conducted by retrograde axoplasmic flow to the cell bodies—as occurs with various injected macromolecules (such as intravenous horseradish peroxidase).<sup>23</sup>

While many neurologists will think that it is inherently improbable that lead will prove to be the primary aetiological agent in motor neurone disease, the findings of this careful study cannot be ignored or dismissed lightly—especially when, in

such a tragic progressive disease, we have no other clues to indicate an alternative, testable, working hypothesis.

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## Health visitors of the future

Most doctors, and other health professionals too, have only a vague picture of the work and skills of health visitors. The success of attachments to general practice has undoubtedly improved relations and led to better mutual understanding, but there are still many family doctors and health visitors who see little of one another despite their professed responsibility for the health of the same people. Health visitors are, however, aware of these uncertainties, and their determination to reduce them is shown by the contents of a booklet<sup>1</sup> published by their statutory supervising body, the Council for the Education and Training of Health Visitors. The council decided four years ago that if health visiting was to progress "the profession must spell out its implicit principles which ultimately predict and guide its practice." Any profession which attempts a statement of the principles on which its practice is based finds it a daunting task—yet without pointers to the future how can health visitors (or doctors for that matter) be confident about their ability to cope with a world in which change is constant and normal?<sup>2</sup>

A working group composed mainly of health visitor tutors began by defining the professional practice of health visiting as "planned activities aimed at the promotion of health and prevention of ill-health"—for health visitors are primarily concerned with helping people to make the most of their health. The borderlines between health and sickness have, says the report, become blurred. Obesity, alcoholism, depression, bereavement, sexual deviations, and strained family relationships are seen nowadays as diseases rather than problems for the individual; moreover, many health problems are induced by the way of life chosen by individuals. The working party argued that health is a value and that health visitors should help people to search for their health needs and meet them. This search must, however, be purposeful and well informed, and health visitors can give explicit help—if they are trained "in logical, critical thinking and in scientific method."

Doctors sometimes fear that an attached health visitor will merely create more work for them, and the working party recognised the undesirability of stimulating people to become aware of needs which cannot be met. One solution is the encouragement of self-help. The report also argues that planned regular visiting has a valuable function in effective, primary prevention. Health visitors also have a part to play as policy makers in health, not only nationally but also within a group practice or primary care team. Yet how effective an influence do the practice health visitors have on what is decided and how it is decided? Are they there as subordinates or do they have the status and responsibility of colleagues able and encouraged to practise policy on prevention?

Many doctors do not understand how well trained the modern health visitor is in educational methods and do not appear to have much faith in preventive work other than antenatal care, immunisation, cervical smears, and contraception. No doubt some of this scepticism is due to unfounded overstated claims for the success of prevention, but at least as much must be laid at the door of medical educators who have not responded to, for instance, the challenge of preventing ischaemic heart disease. This timely self-examination of the principles of health visiting deserves the serious attention of all who accept health as a value and who believe that prevention needs more emphasis by all health professionals.

<sup>1</sup> *An Investigation into the Principles of Health Visiting*. London, Council for the Education and Training of Health Visitors, 1977.

<sup>2</sup> Royal Commission on Medical Education 1965-68 (chairman Lord Todd). London, HMSO, 1968.

## Treatment with bile acids

Chenodeoxycholic acid taken by mouth dissolves cholesterol gall stones<sup>1-3</sup> and may also prevent their formation<sup>4</sup> and recurrence.<sup>5</sup> It seems also to reduce biliary symptoms and the frequency of relapsing cholangitis and to reduce serum triglyceride concentrations,<sup>6</sup> especially when these were originally raised.<sup>7-9</sup> Other less plausible claims have been made for chenodeoxycholic acid in migraine and rheumatoid arthritis and as an appetite suppressant.

Among the other bile acids, neither cholic nor deoxycholic acid dissolves gall stones when taken by mouth. Deoxycholic acid reduces serum cholesterol concentrations but has no effect on biliary cholesterol.<sup>10,11</sup> Local infusions of cholic acid have proved effective in dissolving stones in the common bile duct,<sup>12-14</sup> but with unacceptably frequent side effects<sup>12</sup>—and not necessarily with any greater success than more bland infusates.<sup>15</sup>

What we have yet to decide is the optimal dose of chenodeoxycholic acid for the dissolution of gall stones. The two large British series<sup>5,16</sup> suggested that doses of about 1 g (15 mg/kg) daily were needed for a satisfactory response rate, but good results have also been reported with lower and less toxic doses.<sup>17-19</sup> Some of the questions about optimum dosage, symptomatic benefit, and other metabolic effects should be answered by the United States National Co-operative Gallstone Study.<sup>20</sup> This is a large multicentre double-blind prospective trial of placebo and chenodeoxycholic acid, 375 and 750 mg daily, whose results may be expected in two years' time. In the meantime patients will need to be carefully chosen, for treatment may need to be prolonged or even permanent. Diarrhoea is common with larger doses, and good results can be expected only if patients are supervised by specialists able to gain experience with this expensive new agent (£13.50 for 12.5 g, or about £1 a day for effective dosage).

At a recent symposium on the biological effects of bile acids

held in Freiburg attention was given to ways of increasing the therapeutic efficacy. Reuben recommended reduction of weight in obese patients and Maudgal suggested a low-animal-fat, low-cholesterol diet, together with single-dose treatment given at night. The use of plant sterols as adjuvant treatment had produced conflicting results. Much interest at the conference was focused on the 7 $\beta$ -isomer of chenodeoxycholic acid, ursodeoxycholic acid, which is present in man only in small amounts in health. This agent has been used empirically in Japan for many years as a hepatobiliary tonic. With the discovery that chenodeoxycholic acid could dissolve gall stones ursodeoxycholic acid has been subjected to a more critical appraisal. Whereas effective doses of chenodeoxycholic acid lead to a heavy preponderance of this bile acid in bile, similar doses of ursodeoxycholic acid increase its proportion to only about half of the total biliary bile acids. In contrast to the equivocal effect of chenodeoxycholic acid ursodeoxycholic acid clearly expands the bile acid pool. Schersten, Stiehl, and Thistle all reported that ursodeoxycholic acid was more potent than similar doses of chenodeoxycholic acid in reducing the cholesterol content of bile, though there was no definite evidence of greater efficacy. Equivalent effects on bile cholesterol content were produced by doses of ursodeoxycholic acid half to two-thirds of those of chenodeoxycholic acid.

Carey drew attention to a complication in the comparison of the effects of these dihydroxy bile acids on cholesterol saturation, in that the presence of large amounts of ursodeoxycholic acid in bile alters its micellar solubility characteristics. Biliary lipid analysis, however, provides only an indication of the success which may be expected. The crucial measure is the effect on gallstones. Most experience with ursodeoxycholic acid comes from Japan. Kameda reported that 600 mg daily was more effective than 150 mg daily, though another group from Tokyo and one published report<sup>21</sup> found no difference between high and low doses. Another puzzling feature of Japanese studies is the response frequently claimed with calcified stones,<sup>22</sup> which are generally believed to be resistant to treatment with chenodeoxycholic acid.

When adequate treatment is given, both chenodeoxycholic and ursodeoxycholic acids can probably dissolve about half of all lucent gall bladder stones. Ursodeoxycholic acid seems to require lower doses that do not cause either the diarrhoea or the mild rise in serum concentrations of aspartate aminotransferase seen with chenodeoxycholic acid.<sup>23</sup> Chadwick reported that the absence of any laxative effect might make ursodeoxycholic acid uniquely useful in steatorrhoea induced by bile acid deficiency. If these advantages can be confirmed in the current European and American studies it may well become the agent of first choice for gallstone dissolution.

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