Lancet i, 910 (1983)

Methanol 910

THE LANCET

Multiple sclerosis

Methanol

Treatment of Multiple Sclerosis

THE history of treatment in multiple sclerosis (MS) is one of recurrent claims for success, each enjoying a brief period of enthusiasm but bringing eventual disappointment to sufferers from the disease. At present most patients receive nothing, dietary supplements, or intermittent courses of corticotropin. The diagnosis of MS can be made early if clinical methods are supplemented with laboratory techniques, and accurate diagnosis should soon be possible in most patients during their presenting clinical episode. Early diagnosis, however, is of little value without an effective treatment, and assessment of therapy is far from easy: placebo factors operate, the natural history of the disease is variable, many symptoms are subjective, objective scoring systems depend mainly on motor involvement, and activity of the disease process is not necessarily reflected by clinical signs.

Fischer et al[1] have added to previous anecdotal reports the results of a placebo-controlled double-blind study of 40 patients with advanced chronic MS treated with 100% oxygen at two atmospheres pressure for 90 min on twenty occasions over 4 weeks. Improvement was seen in 12/17 patients during treatment but was maintained in only 5 after a further 12 months. There was an inverse relation between response to treatment and disability at onset. 2 control patients improved; the others remained unchanged during treatment but thereafter the placebo group deteriorated so that the difference between the two groups in mean disability on the Kurtzke scale, present at completion of treatment, remained significant at 12 months. Apart from transient changes in vision and sensations of pressure in the ears, hyperbaric oxygen had no ill effects. In theory, hyperbaric oxygen might act by reducing oedema[2] or through an immunosuppressive effect,[3] but Fischer and his colleagues suggest that it improves symptoms by raising partial venous oxygen pressure and reducing hypoxic oligodendrocyte damage. On the basis of clinical similiarities between decompression sickness and demonstration of demyelination after fat embolism, James[4] earlier suggested that plaques in patients with MS represent areas of transient venous occlusion due to fat embolism, causing regional hypoxia; he too advocated treatment with hyperbaric oxygen. Action for Research into Multiple Sclerosis (ARMS) has since conducted, prepared, and circulated the first report[5] on a study of hyperbaric oxygen in 38 self-selected British patients. An independent neurologist confirmed that all but 1 probably had MS, of widely differing duration and severity. After treatment 2/12 with progressive disease improved on the Kurtzke scale as did 2/25 with recent relapses, both of whom subsequently deteriorated. The same report contains an assessment by the patients themselves. At the start, they registered 337 symptoms in eleven categories—roughly twice the number documented by the neurologist—and at follow-up improvement was reported in 39%, no change in 54%, and deterioration in 7%. Balance, mobility, and urinary symptoms were the features showing most benefit. The patients were unequivocaly enthusiastic about this treatment, and widespread reporting has led many others to seek it. Hyperbaric tanks are available in many hospitals; self-help groups are being encouraged to establish their own treatment centres at an annual cost of many thousands of pounds and fund-raising has started in several areas. The Multiple Sclerosis Society is planning an independently assessed multicentre controlled trial of hyperbaric oxygen in MS.

Epidemiological evidence suggests that an environmental agent initiates MS in genetically susceptible individuals but direct evidence implicating a virus is lacking. Because of its role in viral infection and because of reports of deficient interferon production and natural killer cell activity in peripheral blood and cerebrospinal fluid from patients with MS, particularly during periods of disease activity, interferon has been used to treat the disease. 10 patients who received thirteen intrathecal injections of partly purified interferon-B over 6 months had fewer relapses in the subsequent year than in the pretreatment period and they did significantly better in terms of disability and relapse rate than did controls (who did not have lumbar punctures).[6] The rationale for use of interferon

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and the claims for its success have been criticised;[7] further trials are in progress.

Various antigens stimulate synthesis of IgG in the central nervous system in patients with MS[8] and during periods of disease activity there are alterations in ratios of non-specific immunoregulatory cells in peripheral blood.[9] On existing evidence it seems likely that MS is primarily a disease of disordered immune regulation in which many agents precipitate attacks; therefore non-specific immunological treatment, given before disability has become serious, may beneficially alter the subsequent course of the disease. Mertin et al[10] treated 43 patients from the United Kingdom with combined immunosuppression in a placebo-controlled double-blind study; immunosuppressed patients showed fewer relapses during treatment and a longer interval between discontinuation of treatment and the next episode; the effect on rate of disability was less impressive. Changes in mitogen responsiveness of peripheral blood lymphocytes seen as the disease progressed in controls did not occur after immunosuppression and treated patients had less deterioration than controls in visual evoked potentials. The presence of HLA-A3 was associated with an increased number of relapses in the control group but this difference was no longer seen in immunosuppressed patients. More convincing evidence that the short-term clinical course of MS can be modified by immunosuppression is provided by a study from the United States[11] in which 58 patients with severe progressive MS received either courses of intravenous corticotropin alone or corticotropin combined with high-dose intravenous cyclophosphamide or with plasma exchange and low-dose oral cyclophosphamide. 16/20 patients treated with high-dose cyclophosphamide remained stable or had improved one year after treatment compared with 9/18 and 4/20 of those treated by plasma exchange or corticotropin alone. The short-term benefits of high-dose immunosuppression were not maintained in the subsequent 2 years but patients responded to re-treatment. No serious complications occurred in this group but they all had transient complete scalp hair loss. Helper/suppressor lymphocyte ratios were abnormal in about half the patients initially and were most likely to return to normal in those treated with high-dose cyclophosphamide; persistent lymphocyte abnormalities were associated with poor therapeutic response. Short-term benefits, perhaps related to removal of circulating factors which block conduction in the central nervous system,[12] are seen after plasma exchange but the long-term effects of immunosuppression plus plasma exchange do not differ from those of azathioprine alone.[13]

Opinions will differ amongst patients and doctors on the relative merits of these forms of treatment. There are many gaps in our understanding of MS so that almost any hypothesis can be fitted to the known facts and used to support a wide range of treatments. The effect of certain immunosuppressive regimens on inducer and suppressor components of the immune system seems inappropriate;[14] and patients may regard hair loss, cystitis, and other complications as too high a price to pay for limited therapeutic success. We cannot say whether elaborate forms of oxygen and other treatments have more to offer than corticotropin with its short-term efficacy. It is well to remember that in about 30% of patients MS runs a benign course[15] over several decades and does not need any form of treatment. In therapeutic trials research workers will depend increasingly on serial measurements with electrophysiological, immunological, and imaging techniques to assess changes in disease activity—methods which will demand great commitment from the patients who offer themselves for inclusion.

Methanol Poisoning

EVEN with energetic treatment the overall mortality of methanol poisoning is about 20% and a similar proportion of survivors have residual visual impairment.[1] The minimum lethal dose in man is of the order of 30 g. After ingestion, methanol is metabolised principally by hepatic alcohol and aldehyde dehydrogenases to the toxic metabolites formaldehyde and formate. The mortality rate is related to both duration and severity of the metabolic acidosis[2] which develops after a latent period of 8–12 hours. Blood concentrations of methanol have less prognostic value, particularly in the context of treatment or if the patient presents late.[2] Typically, the patient poisoned with methanol is confused and ataxic, complains of visual disturbance, epigastric pain, and vomiting, followed later by a metabolic acidosis. Coma up to grade IV (Edinburgh scale) occurs in severe cases.

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Ophthalmoscopy may reveal a concentric field defect with pale oedematous discs. Necrosis of the putamen has been demonstrated both in life by computed tomography and at post mortem.[3]

The identification of alcohol and aldehyde dehydrogenases in the retina (necessary for the interconversion of retinol and retinal) led to a longstanding belief that local formation of formaldehyde in the retina is responsible for ocular toxicity. The evidence, however, is slender. Work in susceptible species of monkeys now suggests that formaldehyde does not accumulate after methanol administration[4] and the methanol ocular toxicity syndrome was reproduced by infusion of formate in monkeys maintained in normal acid-base balance. The prevention of formate accumulation in methanol-poisoned patients may protect against ocular damage.

The nature of the metabolic acidosis has also been under discussion. Smith et al[5,6] described a patient poisoned with methanol who had a combined severe lactate and formate acidosis (blood pH 6·78) and they proposed that lactate accumulation was the result of depression of the hepatic $NAD^+/NADH$ ratio by methanol oxidation. Although lactate accumulation has also been shown by Roe[7] and by Gonda et al,[1] it is surprising that so few other reports of methanol poisoning include measurement of lactate. Another severely acidotic patient, reported by McMartin et al,[8] had a plasma formate concentration sufficient to account for 60% of the excess anion gap at pH 6·83. On the other hand, Sejersted and co-workers have described a series of nine patients in whom plasma formate concentrations alone were sufficient to account for the increased anion gap.[9,10] Blood pH values ranged from 7·16 to 7·35 and thus reflected much less severe acidosis than that in the case of Smith et al.[5,6] Neither Sejersted's group nor McMartin et al measured lactate concentrations in their patients. The most reasonable explanation of this apparent conflict of views lies in the fact that hepatic handling of lactate is pH dependent, the liver becoming an organ of lactate production at pH levels less than 7·0.[11] This effect is well recognised in severe diabetic ketoacidosis.[12] Lactate production will thus be a feature of severely acidotic patients but will be less prominent in those with a lesser disturbance.

Conventional treatment of methanol poisoning is directed towards, firstly, the correction of the metabolic acidosis; secondly, the inhibition of methanol oxidation; and, thirdly, the removal of circulating concentrations of methanol and its toxic metabolites. From a management point of view, the precise nature of the accumulated anions is irrelevant, since it is the solvated hydrogen ions which account for the deaths. Therapeutic efforts must therefore be directed to provision of substantial quantities of buffer base—usually bicarbonate—for their disposal. It should be remembered that the large amounts of bicarbonate, often as much as 2 mol, are accompanied by sodium, with consequent hypernatraemia and hypervolaemia. Haemodialysis should therefore be started as soon as possible. It removes both methanol and formate;[8,13] in addition, it will assist in the correction of the acidosis and will allow removal of excess sodium and water (if necessary, by ultrafiltration techniques). Peritoneal dialysis is only one-eighth as effective as haemodialysis in removing methanol.[14] Dialysis is indicated when a patient has metabolic acidosis, mental, visual, or fundoscopic abnormalities attributable to methanol, a blood methanol concentration greater than 0·5 g/l, or has ingested more than 30 g.

The time-honoured manoeuvre of giving ethanol to inhibit methanol oxidation has an attractive theoretical basis. Some workers, however, believe that ethanol may exacerbate an already severe acidosis.[5,6] Lactic acidosis, sometimes severe, is known to arise in the occasional patient given parenteral ethanol for other reasons.[15] Although there has been no systematic study of its efficacy in patients with an established acidosis, it is clear that ethanol inhibits methanol oxidation when taken concurrently with methanol or given early in poisoning.[16] However, in 28 patients reported from Papua New Guinea[17] who were treated with bicarbonate alone and did not receive ethanol or dialysis, the morbidity and mortality were not dissimilar from those in patients treated intensively with all these measures.

Work in laboratory animals suggests that the susceptibility of primates, including man, to the toxic effects of methanol is due to the absence of a folate-dependent one-carbon pool pathway for the metabolism of formaldehyde and formate to carbon dioxide. Rats are able to oxidise methanol without accumulation of formate or the development of a metabolic acidosis. Folate-deficient rats, however, show the same toxic effects as man.[18] Conversely, administration of folinic acid to

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monkeys susceptible to methanol poisoning prevents toxic effects. Folinic acid administration may therefore be a useful immediate measure in methanol poisoning. An alternative approach to infusion of ethanol has been advocated. 4-Methylpyrazole inhibits methanol oxidation and has been used experimentally, with few toxic effects, to modify ethanol metabolism in man.[19] Furthermore it has proved effective for treatment of methanol poisoning in susceptible monkeys;[20] so there is a good case for investigative use in man.[21]

LEAD IN PETROL: A LONG FAREWELL

"... the only way of ensuring that children are not affected by lead pollution is to phase out the use of lead in petrol". Last week's utterance, from the deputy chairman of the Campaign for Lead-free Air,[1] on CLEAR's position on the lead-in-petrol issue, was still being perused when something much more weighty appeared—the ninth report from the Royal Commission on Environmental Pollution.[2] The Royal Commission concludes that war should be declared on lead on several fronts, one of which is petrol. Prof T. R. E. Southwood and his colleagues had planned a more general review, along the lines of the 1974 report *Pollution Control: Progress and Problems*, but were persuaded to take on lead as a separate and urgent task. This Royal Commission, set up as a standing body in 1970, has as its concern the environment and not, directly, human health. Thus evidence was invited on the suffering of swans swallowing anglers' weights, but not on the effects on human health of lead at low concentrations. Well trodden this ground may be[3,4] but the proportion of this otherwise substantial report that is devoted to human health is disappointingly small. Is the relation between lead (in teeth or blood) and psychometric indices causal, due to confounding factors, or a bit of both? The Royal Commission does not know, but the effect "is at the most small". Anyway it dodges the issue. "The average blood lead concentration in the population is about one quarter of that at which symptoms of frank poisoning may occasionally occur. We find this disturbing." In short the safety margin is too small, and the proper response to this is more urgent action on lead water pipes, paint, industrial emissions, petrol, and other sources.

Earlier this month the Department of the Environment took the unusual step of issuing in summary, three days before they were to be delivered, papers read to the British Psychological Society which show no significant lead effects in children from inner city areas. As has been suspected,[4] when social factors are properly taken into account indices of body lead burden in children are not consistently related to indices of intelligence and behaviour. This is illustrated by Mr Peter Harvey and colleagues' work on 189 2½-year-old children in inner Birmingham. None had a blood lead above 30 μg/dl (the mean was 15·55) and the inverse correlation between blood lead and IQ disappeared when social factors were allowed for.

One of the biggest problems that the Royal Commission faced is the uncertainty over the relative sources of lead in the total body burden. Almost all the lead found in air comes from exhaust emissions but the contribution of this to dust (and alone the circulation[5]) and the role dust and children's hands play in total lead intake are much less certain. As a result a 2-year-old not living in a city might have between as much as 64% or as little as 5% of his or her daily lead intake from petrol, depending on whether petrol contributes all of the lead in dust or none of it.

Reducing lead in petrol to 0·15 g/l (the current UK target) would more than halve lead emissions in exhausts: below this lead additives would be of no value (except to lubricate valves). In the end—while recognising the implications for the motorist, oil refineries, energy consumption, and car manufacturers—the Royal Commission opts for a phasing out of lead additives (by 1990 for new cars), this being achieved through adjustment to a lower octane rating rather than through alternative anti-knock agents or fuels. A stumbling block on the calendar is the European Economic Community: when legislating on lead in petrol, under Article 100 of the Treaty of Rome, which covers preventive medicine, the EEC, instead of contenting itself with a maximum also appeased trade interests with a minimum. CLEAR and others thought they had a way round this, via another article in the Treaty of Rome. Not so says the Royal Commission: once the EEC has legislated under Article 100 that takes precedence. The UK Government has promised immediate action on several recommendations and accepts the phasing out recommendation with no commitment as to timetable. As urged, the UK is to ask the EEC to look at the offending directive again.

PERCEPTION OF BREATHLESSNESS IN ASTHMA

SOME asthmatics seem much more aware of dyspnoea than others, despite similar degrees of airway obstruction.[1] This observation has experimental support from studies in which external resistive loads have been incorporated in the airway: asthmatics vary considerably in their ability to detect such resistive loads. In clinical terms this can, at one extreme, lead patients with only mild asthma to take inappropriate amounts of medication, whilst at the other, severe or even dangerous bronchospasm may develop without causing discomfort.

Campbell and his colleagues in London, Ontario, have for many years been tackling the difficulties inherent in studying the sensation of breathlessness and they have now produced an intriguing analysis of the perception of dyspnoea by asthmatics.[3] Using the standard research technique of histamine provocation for the quantification of bronchial reactivity,[4] they correlated the fall in forced expiratory

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