Journal of Neurology, Neurosurgery, and Psychiatry, 1981, **44**, 1–8

Commentary on Contemporary Neurotoxicity

Toxic substances and the nervous system: the role of clinical observation*

PAMELA M LE QUESNE

From the MRC Toxicology Unit, Carshalton, Surrey and the Department of Neurological Studies, The Middlesex Hospital, London

This paper describes various neurological diseases produced by metals to illustrate the common ways in which toxic disorders arise in our modern environment. At the turn of the century anyone interested in neurotoxicity of metals would probably have studied inorganic lead, inorganic mercury and arsenic as occupational hazards. Although control of exposure is still important, it is a triumph of public conscience and government legislation that neurological disorders due to these metals are virtually non-existent in this country today. I do not propose to consider them further. Nowadays, our environment is poisoned, doctors poison their patients and people poison themselves to such an extent that more toxic illnesses occur today than during the height of the industrial revolution. I will discuss a few examples.

Aluminium

In 1962, McLaughlin *et al*[1] described a patient who had worked for 13½ years in an aluminium powder factory. He developed left sided focal epilepsy, hesitancy of speech and his wife noticed that he was becoming forgetful. Over the next few months he became increasingly demented, had more frequent epilepsy and then died of bronchopneumonia. At autopsy he had a fibrotic reaction to aluminium in his lungs. No gross or microscopic abnormality was demonstrated in his brain, but the aluminium content was considerably elevated. Although almost unique, I have described this patient in some detail because his disease subsequently turned out to be more significant than was thought at the time.

Ten years later, Alfrey *et al*[2] first described a progressive cerebral disorder in some patients undergoing chronic dialysis for renal failure. It was characterised by speech difficulty, progressive dementia, myoclonus, epilepsy which might be focal and focal neurological signs; features similar to those in the patient described by McLaughlin *et al*.[1] By 1976 measurements of aluminium by flameless atomic absorption spectrometry had been developed to the point at which physiological levels could be measured. Alfrey, Le Gendre and Kaehny[3] found a higher than normal aluminium level in grey matter of patients who had died with dialysis encephalopathy (fig 1). Initially this was thought to come from aluminium containing phosphate binding gels commonly used in the management of patients undergoing chronic dialysis. However, the incidence of the disease

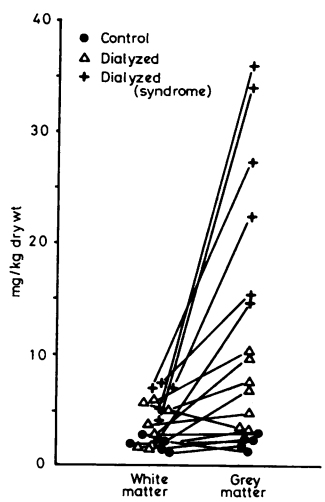

Fig 1 *Aluminium levels in grey and white matter of control subjects and uremic patients with and without dialysis encephalopathy. From reference 3.*

*Based on the Third Pewterers Lecture delivered at the Institute of Neurology, Queen Square, London on 6 March 1980.

Address for reprint requests: Dr PM Le Quesne, Department of Neurological Studies, The Middlesex Hospital Medical School, London W1N 8AA.

Accepted 14 August 1980.

correlated poorly with aluminium consumption in this form.

At about the same time Flendrig, Kruis and Das[4] reported a remarkable difference in the incidence of dialysis encephalopathy in two hospitals in the same city in Holland where apparently identical methods of treatment were used. It was discovered that aluminium anodes had been put into the boiler to protect against corrosion in the hospital where encephalopathy occurred. When the unit moved to a hospital with a different boiler system the syndrome disappeared. This episode focused attention on the water used for dialysis, rather than medication, as a source of aluminium, confirmed by further epidemiological studies. In patients on home dialysis in Scotland high blood aluminium and dialysis encephalopathy were found where the aluminium concentration of the water was high.[5] A larger survey published from Newcastle of 1293 patients from 18 dialysis centres in Great Britain showed a close correlation between the incidence of dialysis encephalopathy and aluminium content of water used to prepare dialysate.[6] In Newcastle where the syndrome used to be common, no further cases have occurred since dialysate water has been treated by deionisation or reverse osmosis (Kerr, personal communication). This episode illustrates the point that today side effects of therapy may be commoner than intoxication from industrial exposure (for example the almost unique case described by McLaughlin *et al*[1]).

It would be wrong to leave the subject of aluminium without a few words about Alzheimer's disease. In 1965 Klatzo, Wisniewski and Streicher[7] produced neurofibrillary tangles by injecting aluminium into rabbits' brain and the question was immediately asked as to whether these had any relation to the neurofibrillary tangles of Alzheimer's disease. The unresolved discussion has continued for 15 years with Crapper and colleagues from Toronto in favour of an association and the Terry, Wisniewski group increasingly against. Crapper and Dalton[8] have produced memory defects and neurofibrillary degeneration in cats by intracerebral injection of aluminium. Crapper, Krishnan and Quittkat[9] found raised aluminium levels in brains from patients with Alzheimer's disease. This finding was not confirmed in a further study by McDermott *et al.*[10] However, the control material from their old patients without dementia was later found to contain neurofibrillary tangles,[11] so that the significance of their results is doubtful.

The main argument against a role of aluminium in Alzheimer's disease is that the neurofibrillary tangles in the disease differ from those induced experimentally by aluminium. Paired helical filaments occur in Alzheimer's disease, first described by Kidd[12] in 1964; aluminium induces 100Å filaments with a different EM appearance.[13] The difference is not merely a species effect because Crapper et al[14] have found that aluminimum produces 100Å and not paired helical filaments in human neurone cultures. Clinically Alzheimer's disease does not resemble dialysis encephalopathy or the disease in the patient described by McLaughlin *et al.*[1] However, this could possibly be due to the difference in tempo of the diseases. Investigation of the problem is continuing. Perl and Brody[15] using scanning electron microscopy with X-ray spectrometry, have demonstrated that tangle-bearing neurones from Alzheimer's disease contain aluminium within the nuclear region whereas neurones without tangles and those from control material contain no aluminium.

In summary, most people do not think that senile dementia is due to aluminium poisoning from an environmental source. A leading article in the *Lancet*[16] in 1976 concluded "the saucepans have little to worry about". However, it is worth considering whether some abnormality of aluminium metabolism might be present, either secondary to the disease process or even a significant part of the disease, whose unravelling might provide a clue to the cause of the disease.

Organotin compounds

In 1954 Dr Barnes and co-workers Stoner and Duff at the MRC Toxicology Unit, Carshalton became interested in the toxicity of organotin compounds because they were beginning to be used in stabilising polyvinyl chloride and in protecting wood, paper and paints from bacteria and moulds. They demonstrated that triethyltin was remarkably neurotoxic.[17] Many other organotin compounds including those now used industrially are not toxic. While this work was in progress, an epidemic occurred in France as a result of which we have an extensive knowledge of the clinical and pathological features of human triethyltin intoxication.[18] A drug called Stalinon, supposedly consisting of diethyltin diiodide was introduced to treat boils. It contained a variable amount of triethyltin as an impurity; 290 patients who took the drug developed neurological symptoms, of whom 110 died. The clinical features have been summarised by Alajouanine *et al.*[19] Symptoms of headache, photophobia, vomiting and drowsiness were due to raised intracranial pressure. Death occurred in 4–10 days. A proportion of patients

developed a spinal cord lesion consisting of sudden onset of flaccid paraplegia, sensory loss with a distinct upper border and sphincter involvement. The cerebral symptoms mainly recovered but the spinal cord lesion was largely irreversible.

In 1957 Magee, Stoner and Barnes[20] described white matter oedema due to triethyltin and autopsy studies in France confirmed that similar oedema occurs in man.[21] Presumably the spinal cord lesion was due to acute compression when oedema reached a critical stage and so might be expected to be irreversible. During the 1960s further pathological studies with the electron microscope demonstrated that the oedema was located between layers of myelin.[22]

Recently there has been renewed interest in organotin compounds in the MRC Toxicology Unit. Shortly before he died Dr John Barnes became interested again in the toxicity of trimethyltin, because there was a suggestion that the compound could be incorporated into dentures to make them radio-opaque. This compound was known to be neurotoxic, but the relation with cerebral oedema had not been established. It was soon confirmed that the neurotoxicity of trimethyltin, unlike triethyltin, was not due to cerebral oedema.[23] Pathological studies showed bilateral, symmetrical neuronal loss in the hippocampus (largely sparing the Sommer sector), pyriform cortex and amygdaloid nucleus (fig 2). Thus two organotin compounds produce quite different lesions of the nervous system.

Symptoms of trimethyltin toxicity have been described in two chemists, who developed epilepsy with mental confusion, following exposure.[24] Unlike patients intoxicated with triethyltin, they had no papilloedema or other manifestation of raised intracranial pressure, thus suggesting that in man as in the rat trimethyltin neurotoxicity does not depend on the development of cerebral oedema.

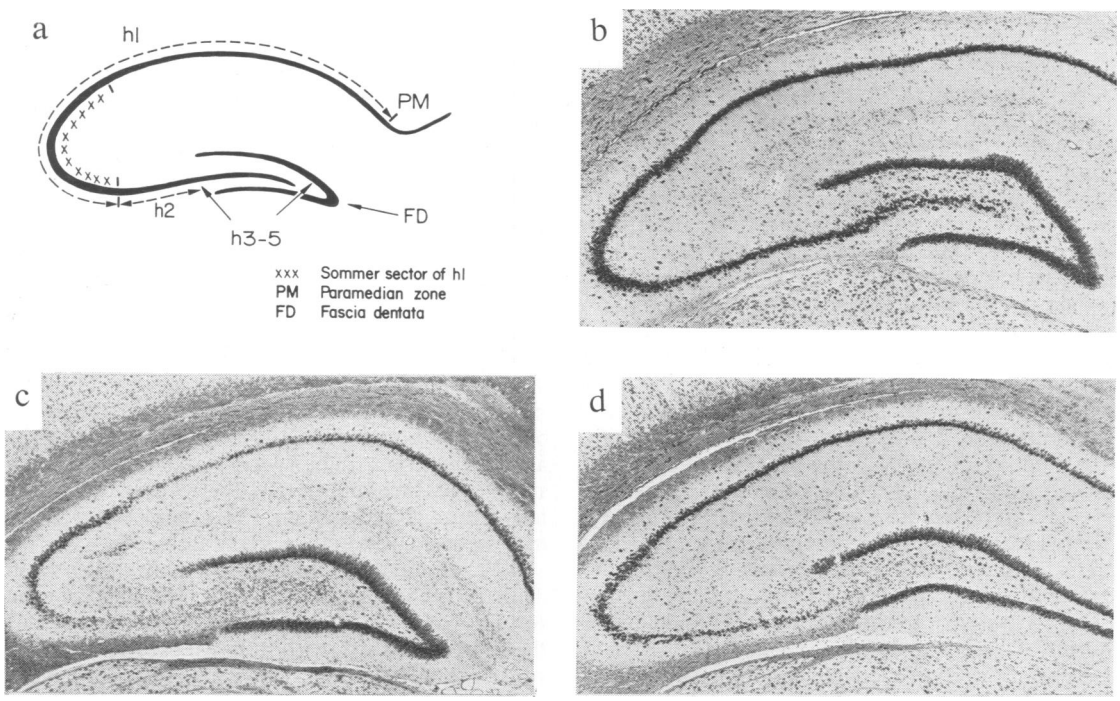

Fig 2 *(a) Schematic diagram of the hippocampus in a coronal plane showing cellular layers. From reference 23. (b) Hippocampus of control rat showing well-stained neurones of the fascia dentata and pyramidal cell band of regions h1–5. Luxol fast blue and cresyl fast violet; × 25. (c) Trimethyltin chloride intoxication. 21 days after a single oral dose of 10 mg/kg. Rat hippocampus showing extensive loss of neurons in h1 (except dorso-lateral portion of Sommer sector), h2 and h3–5. Luxol fast blue and cresyl fast violet; × 23. (d) Triethyl lead acetate intoxication. Following 3 sublethal weekly oral doses of 10 mg/kg. Rat hippocampus showing marked pyramidal cell loss in h3–5 and to lesser extent in h2. Luxol fast blue and cresyl fast violet; × 25.*

Organolead compounds

Tetraethyl-lead became important to toxicologists when it began to be used as an additive to petrol in 1923. Kehoe[25] was the first to delineate the clinical picture of human intoxication in 1925 and immediately recognised that the syndrome was quite different from that produced by inorganic lead intoxication. The earliest abnormality is insomnia, then nightmares, irritability and a maniacal state can develop. Delusions, hallucinations and intense fear can result in attempted suicide. Some indication of the size of the problem in Great Britain can be gained by considering the numbers affected. Twenty-five cases were reported by Cassells and Dodds[26] in 1946 and 15 further cases occurred in five separate incidents over the next 25 years.[27] All were in petrol storage tank cleaners who had taken insufficient precautions against inhalation, the usual cause of intoxication.

Tetraethyl-lead is not toxic in vitro; its effects depend on conversion to triethyl-lead in the liver.[28] Tetra-lead and triethyl-lead produce tremors, hyperexcitability and aggression in rats. In a review of the toxicology of tin compounds in 1959, Barnes and Stoner[18] commented that trimethyltin produced a very similar clinical picture in rats to that produced by triethyl-lead, but different from triethyltin. The different morphological basis for the syndrome produced by the two tin compounds has already been described. Because of the similarity of the syndrome produced by triethyl-lead and trimethyltin, further pathological studies were carried out on rats intoxicated with triethyl-lead at Carshalton. The lesion produced by triethyl-lead had previously been thought to be a reversible biochemical one without morphological change. Seawright *et al*[29] have now described a specific hippocampal lesion following triethyl-lead administration affecting very much the same segments of the hippocampus as trimethyltin (fig 2). Triethyl-lead does, however, produce more widespread damage, particularly in the brain stem.

Data about the effects of limbic lesions in man is scanty and so these toxic lesions should be of interest. Organo-lead toxicity has been thought to be completely reversible in man, but more subtle psychometric testing of previously exposed subjects would be of great interest in view of the permanent neuronal destruction in rats, which also appear to recover clinically from acute intoxication.

One further report is worth mentioning. In 1978 Valpey *et al*[30] described a gasoline sniffing addict who had hallucinations, limb tremor, ataxia and poor memory thought to be due to tetraethyl-lead. He deteriorated and died. At necropsy cerebellar atrophy was found, but the authors also commented on a particularly marked loss of neurones in H 3-4 of Ammons horn in the hippocampus. Thus, at least following chronic exposure, the lesions produced by organo-lead may be similar in man and rats.

Bismuth

During the last six years a new neurological disease has appeared, with which we are unfamiliar in Great Britain. It was first reported from Australia. In 1974 Burns, Thomas and Barron[31] described four patients all of whom had had abdominoperineal resections for carcinoma of the colon, had been treated with oral bismuth subgallate to control colostomy function, and who became confused, unable to walk, and developed myoclonus. All improved when bismuth was stopped. Although blood bismuth concentrations were not estimated in these patients, the relapsing and remitting course of the disease correlated so well with bismuth intake, that the cause seemed fairly certain. In the same year 24 other similar cases were recognised in Australia.[32] At the same time, in 1973 and 1974, the disease rapidly reached epidemic proportions in France[33] where relatively large quantities of bismuth were consumed in the treatment of a variety of chronic colon disorders. Nine hundred and forty two cases of bismuth encephalopathy have now been recorded there with 72 deaths.[34] The full clinical syndrome has been well described from many neurological centres in France. [35 36] There is a prodromal phase lasting weeks or months of depression, anxiety, irritability and possibly mild inco-ordination. Deterioration then occurs rapidly over 24–48 hours with confusion, myoclonic jerks and dysarthria. Inability to stand or walk is a striking feature and partly due to apraxia. Coma may ensue. Recovery may be complete, or there may be mild residual memory loss.

A characteristic bony abnormality has been described consisting of either fracture of the surgical neck of the humerus or osteonecrosis of the humeral head with lesions of the thoracic vertebrae.[36] It is uncertain whether these have a metabolic basis or are secondary to the intense myoclonus.

Blood bismuth estimations have confirmed the cause of the syndrome. The data from one series of patients[37] is shown in fig 3. Greatly elevated levels are found in those with encephalopathy. Patients treated with comparable doses of bismuth who do not develop encephalopathy have levels

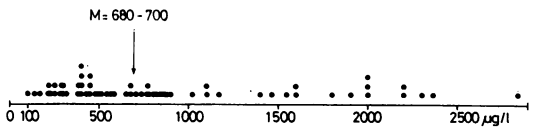

Fig 3 *Bismuth blood levels in subjects with encephalopathy: maximum levels on entering hospital. M—median level. From reference 37.*

less than 50 µg/l. Elevated brain bismuth levels have been found in those who have died.[38]

Many problems arise in seeking an explanation for this disease. Why was it seen predominantly in Australia and France, with only occasional cases in other Western European countries? None have been reported in Great Britain. (Committee on Safety of Medicines, personal communication). Why did the disease appear so suddenly, although there was little change in the amount of bismuth consumed? Bismuth salts are insoluble, so how is bismuth absorbed? None of these questions can be entirely satisfactorily answered at present.

Martin-Bouyer[34] has undertaken an extensive epidemiological investigation of the cases recorded in France. It is clearly established that many different types of bismuth preparation have caused the syndrome, and so one cannot blame a change in manufacturing technique or presence of some new impurity, although it surely cannot be without significance that the Australian cases were caused by bismuth salts imported from France.[39] There is no difference in the dose or duration of therapy amongst subjects who developed encephalopathy and those who did not.[34]

Evidence has been sought that the onset of the epidemic was less explosive than it seemed to be, due to failure in diagnosis before 1973. However, this cannot be confirmed. No bismuth has been found in brains of several patients who died of encephalopathy of unknown cause before 1973. It seems unlikely that patients with such a characteristic clinical disorder would have been forgotten by neurologists who subsequently saw many patients with bismuth encephalopathy. The disease had an uneven geographical distribution even within France. Between 1973 and 1976 the disease spread from the Loire Atlantique region and Paris, eastwards and south across the country. The incidence of the disorder was unrelated to the regional consumption of bismuth.[34]

One theory is that an intestinal microorganism can convert the bismuth salt into an absorbable form, perhaps by methylation, and that spread of this organism determined the spread of the disease.

Organomercury compounds

There is now a vast amount of experimental data about these compounds, but I propose only to consider a few clinical points. The syndrome of paraesthesiae, ataxia and concentric constriction of the visual fields was recognised to be quite different from that resulting from inorganic mercury intoxication when first described by Hunter, Bomford and Russell in 1940.[40]

In recent years methylmercury has become a world wide environmental problem, for two reasons. Inorganic mercury is an important waste product from the large chlor-alkali industry and from paper manufacture. It has on occasions been discharged into rivers or the sea where some is methylated by aquatic microorganisms. As a result methylmercury levels have risen in fish to a point where they have become toxic to man or animals eating them. Such a train of events accounted for the famous outbreak at Minamata Bay in the 1950s,[41] and the later similar episode at Niigata. Much clinical data about human toxicity was derived from these episodes.

The second major cause of human intoxication has resulted from consumption of grain intended for planting which had been treated with methylmercury as a fungicide. The most massive episode of this sort occurred in Iraq in 1971–72 when over 6000 people were admitted to hospital, of whom nearly 500 died.[42] The true incidence of the disorder was undoubtedly much higher than this. As a result of intensive clinical and biochemical studies of the exposed population, a great deal of information has been obtained about methylmercury metabolism and the levels of intoxication likely to produce symptoms in humans.

In fig 4 the incidence of paraesthesia is shown in relation to the estimated body burden of mercury in Iraqis.[43] Clarkson and colleagues consider that the symptoms occurring at low levels of exposure are non-specific and that this represents a background incidence of this particular symptom in the population. A clear increase in incidence which is dose-dependent can be seen at higher levels of exposure. Clarkson *et al*[43] have also been interested in Samoan fishermen who are exposed to methylmercury through the large amount of fish that they eat. Their exposure is constant and methylmercury metabolism has reached a steady state in contrast to the peak exposure in the Iraqis. The incidence of paraesthesiae is unrelated to body burden and similar to the Iraqis with low exposure (fig 4),

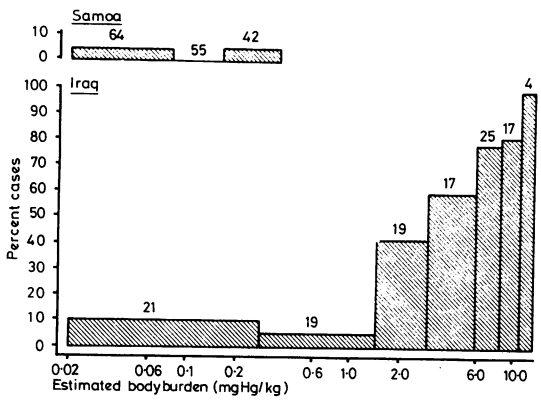

Fig 4 *Histogram indicating the frequency of symptoms of paraesthesiae in Korean contract fishermen based in American Samoa and in the Iraqi population plotted as a function of the estimated body burden. Numbers of subjects in each group are shown in histogram. From reference 43.*

and assumed to be a background incidence. Thus at similar levels of exposure there appears to be no difference in toxic threshold for acute or chronic exposure.

I mention one further study which illustrates how useful it is that methylmercury accumulates in hair and acts as a marker of previous exposure. Iraqi women grow long hair and so the marker remains for some time. By estimating peak mercury levels in mothers' hair, the degree of exposure has been correlated with neurological abnormalities in children who were in utero during the epidemic.[44] The incidence of cerebral palsy in the children increased at maternal peak hair concentrations of 99 ppm. This was a lower figure than had been expected and shows the particular vulnerability of the foetus. The study also confirmed that the neurological syndrome that occurs following exposure in utero is much less specific than that which develops during adult life.

At the time of the episode in Iraq there was some anxiety as to whether it was dangerous to eat large amounts of fish. Much less was then known about human dose-response effects and we felt that a biological way of estimating toxicity would be useful. Cavanagh and Chen[45] had shown that peripheral sensory nerves degenerate early after methylmercury exposure in rats. Since paraesthesiae are an early symptom in man, we thought measurement of sensory nerve action potentials would provide a sensitive index of exposure. Such measurements are sensitive indicators of many types of toxic peripheral nerve damage.[46] Surprisingly the amplitudes of sensory nerve action potentials were normal even in the presence of sensory symptoms and signs[47] suggesting that sensory involvement is due to damage to the central nervous system and not the peripheral nerves. Thus, we concluded that humans respond differently from rats and electrophysiological tests on peripheral nerves are useless for assessing methylmercury toxicity.

Conclusion

Aluminium, organotin, organo-lead, organomercury and bismuth are the metals and their compounds which have been responsible for producing neurological diseases in recent years. Some of these have resulted from therapy, others from isolated episodes of massive environmental contamination or accidental exposure. Vigilance in guarding against occupational diseases is already high. Now we must be aware of the types of hazards I have described and try to devise means of reducing the likelihood of further accidents occurring.

I am grateful to a large number of people for most helpful discussions in preparing this paper. In particular I wish to mention discussions about aluminium with Professor D Kerr of Newcastle and Professor A Davidson, Institute of Neurology, Queen Square; about organotin, organo-lead and organomercury with many members of the MRC Toxicology Unit, particularly Dr N Aldridge, Dr J Cremer, and Dr L Magos. I particularly thank Mr A Brown of the MRC Developmental Neurobiology Unit, Carshalton for the photomicrographs as well as for much helpful discussion. I am also grateful to Dr DO Marsh for discussions and information about organomercury and to Dr G Martin-Boyer who gave me much information about bismuth. My thanks are due also to the authors and publishers of the articles containing figs 1–4 for their permission to publish them. Finally I would like to thank the Worshipful Company of Pewterers for inviting me to give the lecture.

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