Manganese, Parkinson's disease and welders' occupational exposure to manganese – Part 2: Manganese as a neurotoxicological risk to welders

It has been asserted that employment as a welder is associated with an excess risk for the neurological disorder of manganeseism and development of Parkinson's disease at an earlier than usual age. It has been suggested that this may be due to absorption of manganese in emissions from welding processes. In this paper, the second of two parts (part one in “Welding and Cutting” 3/2007), published reports on the incidence of manganeseism and Parkinson's disease in welders and if there being a causal link between these disorders and occupational exposure to manganese compounds are reviewed critically and evidence-based conclusions are drawn.

1 Manganese as a neurotoxin

The brain normally contains very little manganese. When it is present in excess concentrations in the blood it may pass through the blood-brain barrier to accumulate in and cause damage in interconnected groups of specialist cells, the basal ganglia, lying deep within the cerebral hemispheres, far beneath but connected to the cerebral motor cortex. These cells are an essential part of the very complex neurological network which, on a second-to-second basis, controls and coordinates muscle tone, posture and movements. They do this by producing chemical neurotransmitters which by their presence or absence initiate, enhance or inhibit "signals" in the network.

Parkinson's disease and manganeseism are disorders characterised by disturbances of mood, movement, muscle tone and posture – functions which have the basal ganglia at the centre of their control mechanisms. Understandably investigations to understand and provide treatment for these disorders have focused on the basal ganglia and especially on dopamine which, in this respect, seems to be the most critically important of the several neurotransmitters produced.

A recent expert review of the neurotoxicity of manganese [1] provides a useful source of more comprehensive and detailed information than is provided or required here.

2 Parkinson's disease

Degeneration of cells in the areas of the basal ganglia that produce and provide a transfer pathway for dopamine results in diminished supplies of dopamine being provided to receptor cells in response to cortical and other signals. When some 40 to 80% dopamine producing cells and striatal dopamine is lost, clinical signs and symptoms of the mood, muscle tone and movement disturbances which characterise Parkinson's disease first emerge. This is a common and progressive disease which affects 1 to 2% of the population aged 65 and over. Its features are summarised in Table 1 which draws heavily on a recent publication by an eminent neurologist [2].

The underlying cause or causes of the cell dysfunction or destruction are not known and hence the resulting disorder is often called idiopathic Parkinson's disease (IPD). There is good evidence of age being a strongly influential factor and of a familial trait. Manganese has not been shown to damage the cells that produce and transfer dopamine. Indeed, it may be said without fear of contradiction that no convincing evidence has emerged from a
large body of epidemiologic and clinico-pathological investigation of widely varying quality to support the hypothesis that either exposure to manganese or employment as a welder causes or is a risk factor for IPD.

Despite this, the 2001 report of a study which concluded that employment as a welder accelerated the development of Parkinson's disease whereby the welders studied had an average age of onset of the disease of 46 years as against 63 in the control populations [3] sparked controversy which continues to smoulder and flare into litigation proceedings, notably in US courts. No other clinical differences were found and no assertion was made that being a welder caused the disease. All the welders seemed to have idiopathic Parkinson’s disease rather than clinical manganism or other basal ganglia disorders. This report was soon followed by one of a study under the same clinical leadership which concluded that the prevalence of “parkinsonism” was higher within a sample of male Alabama welders than in the general population of male residents in one of the counties in the State [4].

Several aspects of the methods used to achieve the aims of these studies have attracted justified criticism but the suspicions raised cannot be dismissed lightly. A slightly more recent study by a separate group found no relation between welding and the early onset of Parkinson’s disease [5] but, as the authors noted, even this carefully conducted investigation may not be entirely without bias.

Even more recently, studies based on records of welders in Denmark [6] and Sweden [7] demonstrated no differences in the rates for Parkinson’s or other neurological disease, or in the age of first hospitalisation for Parkinson’s, between the welders and the general population of Denmark.

Together these provide probably the largest cohort examined prospectively for the longest period in the history of investigations of neurological disorders in welders and was further enriched by a sub-cohort of shipyard welders. It was, however, unfortunate that welders and flame cutters shared the same occupational classification number in the Swedish study and their disease experience had to be analysed together as they certainly would not have shared the risk of exposure to the same manganese-containing compounds. Overall the investigators found no evidence of increased risks of Parkinson’s disease or other basal ganglia and movement disorders in these occupational groups.

They also broached the subject of the effect of tobacco smoking (which is generally accepted to be associated with a lower prevalence of Parkinson’s disease) and remarked on the higher prevalence of smoking found in Swedish welders compared to men in the general population (42 vs 29%) in a recent study reflecting experience 15 to 20 years earlier [8]. This excess has been remarked upon in other studies. The investigators of the Swedish welders did not have smoking information for their cohort but point out that if this national experience was reflected in their study it may have influenced the prevalence of Parkinson’s disease in welders. Clearly, future investigations should lay emphasis on obtaining smoking data lest a manganese effect on prevalence is masked and passes unnoticed.

### 3 Manganism

Manganese is known to collect specifically in the dopamine receptor cells. When it is present in sufficient concentration it can become toxic to these cells and cause their degeneration. Obviously the cells which have been destroyed can no longer respond to the presence of dopamine and so their normal contribution to signals between and from the basal ganglia is diminished. As remarked earlier, once some 40 to 60% of the receptor cells no longer function features of the movement disorder “clinical manganism” become apparent to the patient and those about him – and usually develop progressively. This rare disorder is similar to Parkinson’s

<table>
<thead>
<tr>
<th>Topic</th>
<th>Clinical manganism</th>
<th>Idiopathic Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history</td>
<td>History of excess occupational or other exposure to manganese.</td>
<td>Possibly a positive family history.</td>
</tr>
<tr>
<td>Early disease</td>
<td>May be prodromal psychiatric “manganese madness” (may be bypassed)</td>
<td>Non-specific complaints including discomfort in the limbs, paraesthesia and fatigue</td>
</tr>
<tr>
<td>Established</td>
<td>Not asymmetric</td>
<td>Asymmetric signs &amp; symptoms</td>
</tr>
<tr>
<td>Disease</td>
<td>Generalised bradykinesia</td>
<td>Generalised bradykinesia</td>
</tr>
<tr>
<td></td>
<td>Widespread rigidity</td>
<td>Widespread rigidity</td>
</tr>
<tr>
<td></td>
<td>Dystonia (may be facial grimacing)</td>
<td>Flexed posture</td>
</tr>
<tr>
<td></td>
<td>Gait dysfunction related to dystonia (“Cook-walk” or stepping broad-based gait with propensity to fall backwards when displaced)</td>
<td>Usually no dystonia except in young patients</td>
</tr>
<tr>
<td></td>
<td>Balance dysfunction with postural instability</td>
<td>Impaired righting reflexes</td>
</tr>
<tr>
<td></td>
<td>Intention tremor</td>
<td>Resting tremor</td>
</tr>
<tr>
<td></td>
<td>Speech Impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micrographia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May improve after removal from exposure</td>
<td></td>
</tr>
</tbody>
</table>

| Pharmacology   | Little if any response to levodopa, While there can be a response in early stages this is not sustained and may be a placebo effect. | Good response to levodopa, Chelation shown to be effective in some cases. Chelation not effective |
| MRI            | As manganese is retained in the brain and is paramagnetic, relevant signal changes may be seen in T1 weighted images in MRI if concentrations are high. | Generally normal                                                                                     |
| F<sup>18</sup>PET | Normal                                                                          | Decreased striatal uptake with most severe changes in the putamen even in the earliest stages of the disease |
| Pathology      | Pallidum and/or striatum                                                          | Substantia nigra, nigrastratal pathway                                                             |
disease in many respects but is sufficiently different to be distinguishable as a separate disease [2]. Note that in PD damage is to the production cells whereas in manganism it is the receptor cells.

Some investigators believe there to be earlier 'subclinical manganism' manifestations which are less apparent and may be revealed only by special tests. The key clinical, pharmacological, imaging and pathological features of clinical manganism are summarised in Table 1.

Hypersusceptibility to this adverse effect of manganese exposure has been recognised very occasionally in the very young, the aged and those with iron deficiency, liver dysfunction or a specific genetic polymorphism.

In contrast to those with Parkinson's disease, patients with manganism do not gain sustained benefit from drug therapy designed to boost dopamine production because, as was remarked earlier, they are not short of the neurotransmitter but rather the ability to respond to it in the damaged areas of the brain. They may benefit from chelation, a chemical procedure which seeks to remove the manganese from cells and prevent further damage.

The accumulation of manganese in the basal ganglia causes a specific appearance on MRI (magnetic resonance imaging) scans. This reduces or resolves when exposure ceases. A second imaging procedure, [18] F-PET (positron emission tomography), which uses a radioactive labelled analogue of the dopamine precursor dopa, is used to indicate the integrity or otherwise of the area of the basal ganglia responsible for the production and transport of dopamine to the receptor areas. Images taken in cases where there has been proven manganese accumulation indicate that these areas have been left intact [2; 9...14]. It may be concluded from this that the accumulation of manganese does not change dopamine production and transport adversely. From this it may be concluded that when manganese accumulation is found in patients with Parkinson's disease it is not the cause of that disease.

4 Clinical manganism in welders

The argument has been put forward that the risk of welders being affected by manganism is negligible or non-existent because:

- the exposure concentration and duration, and thus dose received, is not in the harmful range because of relatively low emissions, the fragmented work pattern of welders and protective measures such as ventilation;
- manganese-compounds in welding fume particles are chemically and structurally more complex and resistant to absorption, and thus less bio-available, than those in dusts produced by the disintegration processes used in industries where it is accepted that manganism has occurred; and
- any absorption of manganese which might be achieved is reduced because of competition with iron in the fume.

The limited evidence from case reports and epidemiological studies has been examined to determine if this bears out that overarching contention.

There were only two workers classified as welders involved over 400 putative cases of manganism in a 1931 review [15] discussed by Whitlock and colleagues in 1996 [16]. Most of the affected workers were exposed over protracted periods in manganese mines and ore mills where manganese-rich dust was formed by disintegration in contrast to the high energy and heat of the arc which is the source of manganese-compound-containing particles in welding fume. Moreover, though exposures to manganese-rich welding fume may have been high, the descriptions of the signs and symptoms of the disorder affecting these two welders do not produce a convincing case for the diagnosis of manganism [17].

By 2005 there had been 24 published reports on studies of clinical manganism of which the 12 listed in Table 2 had identified the disorder as having occurred in a further 45 men classified as welders by the investigators [16; 18...28]. Careful reading of these reports reveals that probably no more than 29 of these 45 "welders" had gained their exposure to manganese compounds from welding as a joining process, Table 2. The others had been employed in other fume emitting electric arc processes such as burning, gouging and cutting, and hard-facing rail tracks.

As shown in Table 3, when the clinical features reported in the literature for the 29 workers who truly had been welding (as defined for the purposes of this review) are related to the criteria for clinical manganism, summarised in Table 1, the evidence for the disease in 24 of them is so scanty and/or bears so little resemblance to or differs in vital ways from these cardinal features that the diagnosis cannot be sustained. The remaining five cases only just cross the threshold of "possibly correct" but no well-founded conclusion on diagnosis or causation can be drawn on the evidence presented. The determination of the cases has been explained in greater detail elsewhere [29].

4.1 Low incidence in welders

Even if all five of these cases were to be substantiated and linked conclusively to welding this would give an exceedingly low incidence of clinical manganism in welders taken against the extensive use of electric arc welding of steel and the huge number of workers who are or have been potentially exposed to manganese-containing welding fumes. That single statistic alone argues loudly against the assertion that welders are or have been at high risk of developing clinical manganism from exposures at work.

In fact, the level of risk has been low and, judging by the evidence presented, scarcely features in welding as a joining process. Yu and his colleagues appear to have been correct when they remarked in 2003 that "there is no confirmed case of welding-fume associated manganism" [30]. There is little to suggest that their observation is not valid in 2007.

5 Subclinical manganism

Studies have been mounted to determine if welders said to have been exposed occupationally to manganese compounds have suffered subclinical damage – that is, have features of neurological damage which might not be apparent to the worker or those around him but would be apparent in the results of such functions as memory, reaction time and fine control of movement [31...34] or in neurophysiological examinations such as electroencephalography (EEG) and measurement of visual evoked potentials (VEP). At least some of the principal neurobehavioural/psy-
The psychological investigations underlying that claim are thought to be flawed, perhaps significantly [35].

The investigators in one neurophysiological study concluded that abnormalities in EEG and VEP found in the youngest welders were sufficiently linked to airborne exposure to manganese and concentrations on manganese in blood as to be suitable for the detection of early effect of exposure to low manganese concentrations [36]. This is an interesting observation as biological monitoring of exposure to manganese is notoriously difficult and unreliable.

Overall the evidence for subclinical manganism related to welding fume is somewhat inconsistent and, to date, not entirely convincing. There may have been damage resulting from other exposures. The brain cells which might be affected in subclinical manganism have not been defined but a recent study which linked increasingly abnormal MRI appearances of the pallidum to decreasing neurobehavioural tests scores [37] may have given a clue.

It is important to investigate the risk of subclinical damage more thoroughly than has been reported to date, regardless of whether or not it may herald the onset of clinical manganism, because even loss of a degree of control of movement could have a significant effect on the function of a high performance welder and on the quality of life of anyone who might be affected.

It may not be prudent to dismiss the cautions by those investigators who advocate further reductions in occupational exposure levels. This view is reflected in the actions taken by health and safety regulatory authorities in several countries to reduce occupational exposure limits for manganese without a totally sound evidence base upon which a programme of prevention and health surveillance might be advised or designed. It will be important that sufficient, appropriately controlled, linked environmental and health effects monitoring is undertaken to determine whether or not these stricter controls are being effective in reducing exposure and preventing subclinical damage. This must be prefaced by validation of a battery of appropriate performance tests.

6 Could clinical manganism and Parkinson's disease develop concurrently?

It is thought prudent to consider if it is biologically feasible for exposure to manganese (as a welder or otherwise) to accelerate the development of Parkinson's disease given that it does not appear to reduce the production or transmission of dopamine.

Could the cell damage which results in the separate disorders of Parkinson's disease and clinical manganism develop concurrently in the different critical areas of the basal ganglia? Should this occur sufficiently to reach critical levels of dysfunction in both areas there would be progressively reduced production of dopamine (the incipient Parkinson's element) occurring at the same time as progressive reduction in the number and capacity of receptor cells to react to dopamine (due to the effects of manganese). In consequence, signs and symptoms of Parkinson's disease might well become apparent earlier in the course of producer cell reduction from whatever cause than would be expected because there would be fewer receptor cells to react to the reduced supply and, overall, neural discharges would be reduced. Thus, if normal ageing is the causal factor in the cell destruction which is producing the Parkinson's disease then that disorder, rather than manganism, could appear at a younger age in those with manganese-related damage of receptor cells than in men and women in the general population in whom receptor cells remain undamaged.

There is, as yet, no direct evidence to support this hypothesis for manganese-accelerated IPD. It gains a degree of credibility from the conclusions of at least two studies, the first where it is postulated that the burden of environmental manganese exposure plays an important role in causing Parkinsonian disturbances by enhancing physiological ageing of the brain [39] and the sec-

### Table 2

<table>
<thead>
<tr>
<th>Source paper</th>
<th>Classified as &quot;welders&quot;</th>
<th>Welding (as defined)</th>
<th>Arc burning, cutting or Gouging, hardfacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oltramare et al</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Whitlock et al</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tanaka &amp; Lieben</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hine &amp; Pasi</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chandra</td>
<td>24</td>
<td>Possibly 14</td>
<td>10 (possibly hardfacing high manganese steel rail track)</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Angle</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Discalzi et al</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sato et al</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ono et al</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sadek et al</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Josephs et al</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Totals</td>
<td>45</td>
<td>29</td>
<td>16</td>
</tr>
</tbody>
</table>

Men classified as "welders" with diagnosis of clinical manganism in literature since 1965 who were welding and using other arc processes.

### Table 3

<table>
<thead>
<tr>
<th>Source paper</th>
<th>Number said to be clinical manganism or manganese-induced parkinsonism</th>
<th>Number assessed by current author (GM) as possibly but not definitely correct by 2007 standards.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oltramare et al</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chandra</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Angle</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Discalzi et al</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sato et al</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ono et al</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sadek et al</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Josephs et al</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>29</td>
<td>5</td>
</tr>
</tbody>
</table>

Comparison of diagnosis of clinical manganism in welders truly engaged in welding, reported in the literature against 2007 standards.
ond, an animal study that showed the effect of manganese on motor function to be enhanced significantly in the presence of chemically-induced pre-Parkinsonian condition [38].

7 Conclusions

We have sought to summarise and assess evidence in the open scientific literature on the risk of welders developing clinical manganeseism, subclinical manganeseism or Parkinson’s disease as the result of occupational exposure to manganese. From this we have concluded that manganese and its inorganic compounds are widely used in many industries and have been accepted as occupational neurotoxins which have caused a distinct and disabling clinical entity, manganeseism, in several types of work, notably where exposure is by way of dust. There is inconclusive and inconsistent evidence that, in some of these occupations, subclinical neurological effects, detectable only by neurobehavioural or neurophysiological tests, may have been caused by low doses. This has prompted a re-evaluation of occupational exposure limits. In recent years some countries have set more stringent levels of protection against exposure.

Whether or not manganese compounds in welding fume cause neurological damage is a matter of contention. It is important to know definitely one way or another because with manganese being an essential component of steel and thus an inevitable constituent of welding fume emitted from steel welding processes, it places welders and those working with them at risk of exposure to these compounds in respirable particles. It is present, in part, in complex oxides (spinels), within a core protected by a silicon oxide shell – as distinct from the much simpler form of particle formed by disintegration in processes such as mining and ore milling where manganese has been diagnosed convincingly. These chemical and physical differences may reduce its bioavailability and the risk presented by exposure to manganese-containing welding fume relative to disintegration processes.

Welders have been recorded as having been exposed to high levels of manganese-containing welding fume, especially where they have worked in confined, unventilated spaces. Even in these situations it appears that exposure levels and dose received are likely to be less than in mining or ore crushing. When care is taken to exclude exposures from hardfacing and burning and cutting arc processes, where manganese may form a high percentage of the welding fume, and attention is focused only on welding as a joining process, manganese compounds may form a relatively low percentage of particles, less than 5% in the alloy, and are much outweighed by iron. Questions of solubility and resulting bioavailability remain unanswered but it does appear that in some circumstances, although the manganese-compound-containing welding fume particles are insoluble in water the compounds in particles retained in the alveoli are absorbed, at least in part, and blood levels of some exposed groups reflect this relative to unexposed workers.

The soundest interim conclusion to be drawn from the evidence on bioavailability and adverse health effects of manganese-containing compounds in welding fume is that more and better evidence is required before any absolutely scientifically-sound conclusions can be drawn.

We have also sought to identify critical gaps in knowledge and the questions these raise and to suggest ways in which the missing information may be gained to allow soundly-based final conclusions to be drawn.

The absence of evidence which was repeatedly apparent in the review excites many questions on the toxicity of manganese and its inorganic compounds in general and especially those emanating from welding processes. These include:

- What are the exposures to manganese experienced by welders from their welding and other processes such as grinding, and from the general workplace background?
- How much manganese in compounds in welding fume is absorbed in the various chemical forms and oxidation states?
- What proportion is bioavailable once it is absorbed?
- How is manganese distributed and what contribution does competing iron make protecting against neurotoxicity?
- What are the mechanisms of neurotoxicity?
- Is there a dose-response relationship for subclinical and clinical effects?
- What absorbed current or cumulative dose is sufficient to enter the brain and cause neurotoxicity?
- If they occur at all, do subclinical effects persist or progress once exposure has ceased?
- Is welding causally related to any forms of manganism?
- If there is no association why is that the case?
- Are effects reversible?
- What biomarkers might be used for routine health surveillance?
- Is employment as a welder associated with premature onset of IPD and, if so, why?

Many of these questions require much better designed and conducted research than in the past, some in the laboratory and clinical and most in epidemiological studies. A huge step forward in that direction would be made by neurologists and other investigators to reach a consensus on the diagnostic criteria for Parkinson’s disease and clinical and subclinical manganeseism and for these to be used unambiguously in clinical and epidemiological studies.

With that in mind, the next step should be to conduct sufficiently powerful case-control and cohort studies with retrospective exposure assessment using a validated method and, as a basis for follow-up studies, create a record of details of current exposures for employed subjects in new cohorts. These studies may well have to be multi-centre, even international, to have sufficient size and thus power to detect statistically significant differences if these actually exist between exposed and unexposed populations.

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