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14. ABSTRACT Inhalation of high manganese (Mn) concentrations may result in serious irreversible neurological disease (manganism). The air exposure level associated with an increased risk of acquiring subtle neurological disturbances is currently not known. Welding fumes contain Mn. In this study 332 subjects have been examined with neurobehavioral methods, of whom 137 are currently exposed welders and 137 are referents. Among these, 63 welders and 65 referents were examined with the same methods around six years earlier. Also 34 patients diagnosed with manganism (17 also examined six years earlier) and 25 with idiopathic Parkinson's disease (PD) were examined. Positron Emission Tomography examinations were carried out in eight PD-patients, eight manganism cases and six referents. The laboratory analyses of the biological samples and personal welding fume samples have been completed. Currently the statistical work is being carried out. The scientific publication process has started.					
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Introduction

Manganese (Mn) is an essential trace element in humans, but inhalation of high Mn concentrations has been associated with irreversible neurological disease (manganism). Welding fumes may contain high amounts of Mn, and cases of manganism among welders are reported every year in Russia. Welders are by number the most important group of workers occupationally exposed to Mn. Exposure to Mn at lower concentrations can result in subtle motor disturbances. The exposure level associated with an increased occurrence of such disturbances is currently not sufficiently known.

Neurobehavioral tests are applied, parameters for iron status are determined and an extensive exposure assessment is carried out in this study. Also PET-scan examinations are carried out in a limited number of subjects. The main objective is to assess the value of selected neurobehavioral tools in an epidemiological study, in order to investigate their sensitivity for detecting subtle neurological functional changes.

Body

A contract was signed between the National Institute of Occupational Health (Norway) (NIOH) and Vanderbilt University (USA) on January 31, 2007, to carry out "A Study of the Nervous System in Welders". In the letter from Vanderbilt University Medical Center to the NIOH dated March 8, 2007, the fully executed original of the contract was received, this date representing the start of the project.

After the original contract was received, preparations for examining the participants were started. Due to software problems of the CATSYS test system, the start of the data collection was delayed by around three months. Altogether 137 welders and 137 age-matched referents have been examined with neurobehavioral tests in a study with cross-sectional design. Among these participants, 63 welders and 65 referents were examined with the same neurobehavioral test battery around six years earlier. Thus, this part of the investigation has a prospective study design. Further, 25 patients with newly diagnosed idiopathic Parkinson's disease (PD) and 34 patients diagnosed with manganism were examined. The latter group consists of former welders, of whom 17 had been examined around six years earlier. In 22 subjects, of whom eight had PD, eight had manganism and six were referents, PET scan examinations were carried out. Whole shift air samples for the determination of welding fume components were collected among the welders. Samples of whole blood, serum and urine were collected. The air samples were dissolved in Hatch solution (artificial "lung lining fluid" prior to analysis. This procedure requires the use of special centrifugation tubes. These were difficult to obtain and this delayed the progress of the project. The determination of trace elements in whole blood with an ICP-MS has been completed at NIOH. The biological samples have been analysed. The first scientific manuscript resulting from the study is under preparation.

The mean age of all examined welders was comparable to that of the referents (Table 2). The level of B-Mn in whole blood is substantially higher in the welders. Also the concentrations of Mn in urine and in serum are significantly higher in the welders. The geometric mean personal air exposure to Mn was $219 \mu\text{g}/\text{m}^3$ (1-3510). Seven welders refused to carry air sampling equipment. The statistical analysis of the neurobehavioral data has started. Preliminary results indicate significant group differences with respect to several of the applied neurobehavioral tests. The differences are mainly observed for the grooved pegboard and finger tapping tests, the digit symbol test and the reporting of subjective symptoms. We have also applied the simple reaction time test, where the welders perform significantly poorer than the referents as a whole. However, further statistical analysis need to be carried out before

firm conclusions can be drawn, and in particular to assess potential dose-response

Table 1 Background variables among all welders and referents examined in 2008/2009

	Welders (N=137)	Referents (N=137)
	Mean[#] (range)	Mean (range)
Age	39.9(19-70)	40.1(19-70)
Years of welding	16.6(1-45)	-
B-Mn (µg/L)	13.9(5.9-40.3)	8.2(4.1-13.9) [†]

[#] Arithmetic mean; [†] Fourteen subjects declined blood sampling

Table 2 shows some key data of the welders and the referents who were examined in 2002/2003 and re-examined in 2008/2009. Data from the original group that was examined in 2002/2003 have been published (Ellingsen et al., 2006; Ellingsen et al., 2007; Ellingsen et al., 2008). The follow up time was nearly identical in the two groups, being slightly shorter than six years. The referents were older than the welders. The contrast in B-Mn between these welders and the referents is quite large, the mean concentration difference being 5.6 µg/L. At the first examination the difference was 1.6 µg/L. The results from the air samples support the impression from the blood samples of higher exposure at follow up when compared to the baseline. Preliminary neurobehavioral results suggest that the welders may have a larger decline in the grooved pegboard test than the referents. It may also further be noticed that a few welders had a substantial decrease in their finger tapping test scores, far beyond what was observed among the referents.

Table 2 Background variables recorded in the subjects that were examined in 2002/2003 and followed up in 2008/2009. Data at follow up.

	Welders (N=63)	Referents (N=65)
	Mean[#] (range)	Mean (range)
Age	42.7(26-70)	45.8(22-70)
Months of follow up	70.8(59-90)	70.7(61-80)
Years of welding	19.5(7-45)	-
B-Mn (µg/L)	13.6	8.0 [†]

[#] Arithmetic mean; [†] Eight subjects declined blood sampling

Altogether 25 subjects diagnosed with PD and 34 subjects (all welders) diagnosed with welding related manganism were examined. One PD patient had in the medical history information about a cerebral ischemic event, and were thus excluded. These subjects underwent the same neurobehavioral test battery as the welders and referents. Again, preliminary results indicate substantial differences between the two groups. Crudely it can be summarized that the PD patients had more tremor, but also different quality of tremor when compared to the manganism patients. This was mainly a shift in the tremor frequency pattern towards lower frequencies, a more regular (pathological) tremor, and a smaller dispersion in the tremor frequencies. The mangansim patients, on the other hand, had more postural sway. There is apparently more side difference in the clinical manifestations in the PD-patients as compared to the manganism patients with respect to neurobehavioral performance. However, the data analysis has not yet been completed, and the results are preliminary.

Eight patients with PD, eight diagnosed with manganism and six referents were examined with PET-scan. The data treatment has not yet been completed, but preliminary

results indicate that the manganism patients predominantly have reduced glucose activity in the head of the nucleus caudatus. This is also the case in the PD patients, but they also have alterations in other brain areas such as thalamus and amygdalae. It could be of some interest that the preliminary data indicate an association between certain neurobehavioral test scores and the reduction of glucose activity in the nucleus caudatus.

The first manuscript from the study is currently under preparation. The main results are referred below. Further manuscripts will be prepared.

SUBSTUDY 1 - Biological monitoring of manganese in welders in relation to the solubility of welding fume components

In this sub-study solubility data of Mn in personally collected welding fume samples are related to individual concentrations of Mn in serum, whole blood and urine. 237 whole-shift welding fume samples were collected. Seven welders refused to carry air sampling equipment. The welding fume was dissolved in Hatch solution to assess the solubility of Mn (and iron) in a simulated lung lining fluid. Only around 12% of the Mn mass contained in the welding fume particles was found to be soluble in the Hatch solution and iron was substantially less soluble than Mn. This is important, because animal studies have shown that intratracheal instillation of soluble $MnCl_2$ or inhalation of soluble $MnSO_4$ resulted in substantially higher striatal Mn concentrations in rats compared to the less soluble MnO_2 or Mn_3O_4 . We observed statistically significantly higher B-Mn, U-Mn and S-Mn in the welders as compared to the referents. The highest Pearson's correlation coefficients between Mn in air samples and Mn in biological samples were obtained for the associations between B-Mn and S-Mn and exposure to soluble Mn two days before the blood sample collection. U-Mn was most highly correlated with soluble air Mn collected the day before the biological sampling. Multiple linear regression analysis also indicated that "years of welding" was associated with B-Mn and S-Mn. Simultaneous exposure to Fe had no statistically significant impact on these associations. The correlations between the Mn concentrations in the biological fluids were all statistically highly significant among the welders, the Pearson's r being between 0.63 and 0.69. The corresponding non-significant associations in the referents were between 0.06 and -0.07. These results suggest that the mobility of Mn between the different compartments are quite different in the welders when compared to the referents. In particular the association between S-Mn and U-Mn could suggest that S-Mn in the welders are bound to ligands that can be filtered in the kidney glomeruli, and that these complexes may be smaller in the welders than in the referents.

Key Research Accomplishments

137 welders, 137 referents, 34 patients diagnosed with welding related manganism and 25 patients with newly diagnosed idiopathic Parkinson's disease (PD) have been examined with neurobehavioral methods. Recruitment to the study has been completed.

Eight patients with manganism, eight with PD and six referents were examined with PET-scan.

237 personal whole shift welding fume samples has been collected.

Blood and urine samples were collected in 315 and 314 subjects, respectively.

Welding fumes were dissolved in a simulated lung lining fluid (Hatch solution). Welding fume components were determined by ICP-MS (soluble in Hatch solution) and ICP-OES (non-soluble in Hatch solution).

Metal analysis in urine, whole blood and serum with ICP-MS has been completed.

Relevant biomarkers in serum have been analyzed.

Reportable Outcomes

Conference abstracts

Ellingsen DG. Neurobehavioral performance of Parkinson's disease patients and welders with the diagnosis of manganism (preliminary results). The Manganese Health Research Program Showcase Conference. New discoveries – New directions. Juni 24-25, 2009. Washington DC, Lansdowne Resort, USA.

Ellingsen DG. Manganese neurotoxicity in welders. 9th ISTERH 2011. Trace elements in health and disease: Essentiality, Toxicity. Rixos Premium Hotel, Belek, Turkey, 16.-21. October 2011.

Ellingsen DG, Zibarev E, Kusraeva Z, Berlinger B, Chashchin M, Chashchin V, Thomassen Y. Biological monitoring of manganese in welders in relation to the solubility of welding fume components. Enviromin 2012, Loskop Dam, Forever Resort, South Africa, March 11-15.

Manuscripts in preparation

Biological monitoring of manganese in welders in relation to the solubility of welding fume components.

Conclusion

The enrollment of subjects to the study has been completed. Altogether 332 subjects have been examined with neurobehavioral methods. The laboratory analyses have been completed. The statistical analyses are currently carried out. Preparation of the first scientific paper has started.

References

Ellingsen DG, Dubeikovskaya L, Dahl K, Chashchin M, Chashchin V, Zibarev E, Thomassen Y. Air exposure assessment and biological monitoring of manganese in welders. J Environ Monit 2006;8:1078-1086.

Ellingsen DG, Chashchin V, Haug E, Chashchin M, Tkachenko V, Lubnina N, Bast-Pettersen R, Thomassen Y. An epidemiological study of reproductive function biomarkers in male welders. Biomarkers 2007;12:497-509.

Ellingsen DG, Konstantinov R, Bast-Pettersen R, Merkurjeva L, Chashchin M, Thomassen Y, Chashchin V. A neurobehavioral study of current and former welders exposed to manganese. NeuroToxicology 2008;29(1):48-59.

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TITLE: Water-Borne Manganese Exposure and Motor Function in Young Adults

PRINCIPAL INVESTIGATOR: Joseph Graziano, PhD

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center
Nashville, TN 37203

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TYPE OF REPORT: Progress report

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14. ABSTRACT The neurotoxicity of Mn in adults with occupational inhalation exposure is well established. The syndrome known as "manganism" is characterized by a Parkinson-like condition with weakness, anorexia, apathy, slowed speech, emotionless facial expression, and slow movement of the limbs. Many issues remain to be determined however, including dose-response relationships, the contribution from non-inhalation sources of Mn exposure, and the impact of nutritional status – particularly iron – on susceptibility to neurologic disease. We propose here to expand an ongoing study in Bangladesh, investigating the consequences of water-borne Mn exposure on motor functioning in young children, 7-9 years of age, to include young adults, 18-21 years of age, i.e., an age group that is representative of young U.S. military personnel. To do this, we will use a well-standardized, individually-administered test of motor function that is normed for children, adolescents and young adults from 4 - 21 years of age, i.e., the Bruininks Oseretsky Test, 2 nd Edition.					
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Body

Summary of Objectives: This project seeks to test the hypothesis that total manganese (Mn) exposure from drinking water and diet may be adversely related to motor function in young adults, 18-21 years of age. The field work took place in Araihasar, Bangladesh, where Mn concentrations in drinking water are variable and often elevated well above the WHO guideline level of 300 ug/L. The project sought to recruit 100 young men and 100 young women, half of whom were consuming water with < 300 ug/L Mn and half above that. Motor function was assessed using an adaptation of the Bruininks-Oseretsky -2 test of motor functioning, a well validated instrument. In addition, a validated dietary survey questionnaire was administered to obtain data on dietary Mn, and a validated questionnaire concerning exercise, a covariate, was administered since exercise influences motor function. Finally, blood measurements of Mn and various parameters of iron metabolism were also carried out.

Project Status: Following piloting of new assessments and training of local staff, field work for the study in Bangladesh was completed in 2010, and laboratory blood measurements have now been completed at Columbia University. Analysis of baseline water samples (at approximate youth age 8-10 years) is complete; analysis of current well water exposure data is expected to be completed by late February, 2012). A total of 100 males and 82 females were successfully recruited and completed the protocol. Data entry for the BOT-2 and dietary survey and the physical activity questionnaire have all been completed. Regression modeling based on current blood measures of exposure has been conducted, although we are awaiting current well water data to complete testing our hypotheses.

Sample description: As Table 1 illustrates, several key measures differed significantly across gender, necessitating separate models for males and females. Baseline water values did not differ across gender. The overall baseline mean water Mn concentration was 912.33 ug/L, and average baseline water As concentration was 31.54 ug/L.

Table 1. Sample Characteristics

	Total sample N=182	Male N=100	Female N=82	
Age	19.22 (0.80)	19.26 (0.79)	19.16 (0.81)	
Married	6.04 (11)	5.00 (5)	7.32 (6)	
Education (years)	7.86 (3.39)	6.96 (3.63)	8.96 (2.70)	p< .0001
Blood measures				
Blood As (ug/L)	5.93 (4.62)	6.46 (4.60)	5.30 (4.58)	p < .02
Blood Mn (ug/L)	14.06 (3.28)	13.15 (2.64)	15.16 (3.65)	p< .0001
Serum ferritin (ng/dl)	49.58 (28.08)	60.12 (30.02)	37.11 (19.36)	p< .0001
Hemoglobin (g/dL)	12.92 (1.36)	13.72 (1.04)	11.94 (1.01)	p< .0001
Baseline exposure				
Water As (ug/L)	31.54 (46.53)	27.85 (38.45)	36.04 (54.72)	--
Water Mn(ug/L)	912.33 (886.61)	802.80 (810.16)	1045.90 (959.91)	--
BOT-2 Std scores				
Fine Manual Control	29.62 (2.81)	29.43 (2.91)	29.84 (2.69)	--
Manual Coordination	43.69 (6.66)	44.43 (6.46)	42.79 (6.83)	--
Body Coordination	38.65 (5.69)	39.71 (5.60)	37.37 (5.55)	p< .01
Strength and Agility	33.61 (2.15)	33.81 (1.99)	33.37 (2.32)	--
Total Motor Composite	33.75 (2.37)	34.22 (2.28)	33.18 (2.36)	p< .005

Key Research Accomplishments

Laboratory measurements of all blood and urine parameters have been completed, and preliminary analyses based on current blood exposure markers have been conducted. Multiple regression models based on log-transformed hematologic measures of exposure consider males and females separately, and adjust for maternal education, serum ferritin and hemoglobin concentration. Neither dietary Mn nor exercise history contributed to measures of motor function. Table 2 presents results of these analyses, demonstrating different patterns for males and females. Adjusting for other features, females' Fine Manual Control showed modest, albeit significant, negative associations with blood As concentrations, while Body Coordination showed substantial negative associations with blood Mn concentrations, but only for males.

The strongest associations for Mn exposure were for Body Coordination items in males (a similar, though not statistically significant, pattern appeared for females). Test items on this subscale include those measuring balance and bilateral coordination. For every log unit of BMn, males showed a 7-point decrement in Body Coordination scores.

Table 2. Models predicting BOT scores for males and females

	Fine Manual Control		Manual Coordination	
	Males (B)	Females (B)	Males (B)	Females (B)
Maternal Education	0.27	1.42 *	1.17	2.62
Serum Ferritin	-0.07	0.51 **	0.49	0.05
Hemoglobin	0.87	-0.10	1.53*	-1.68*
Log Blood As	-0.46	-0.04*	-1.60	-0.46
Log Blood Mn	-0.80	1.84	0.34	0.72
R sq	1%	20%	10%	11%

	Body Coordination		Strength/Agility	
	Males (B)	Females (B)	Males (B)	Females (B)
Maternal Education	2.23	1.1.56	0.25	0.37
Serum Ferritin	-0.07	-0.32	0.10	0.32
Hemoglobin	-0.07	-0.81 0.24		0.09
Log Blood As	-0.70	0.52	-0.29	-0.19
Log Blood Mn	-9.12**	2.83	-0.95	-1.42
R sq	11%	4%	3%	10%

* p < .05; ** p < .01

Reportable Outcomes

Conclusions and Publications: No conclusions have yet been reached, as we await final analyses of current water data. We plan to submit an abstract to the annual meeting of the Superfund Research Program by August 15th.

Projected completion: We anticipate that the final statistical analyses will be completed by late February, 2012, and that our first manuscript will be submitted for publication shortly thereafter.

Current faculty who received support from the grant:

- Joseph Graziano, PhD
- Gail Wasserman, PhD
- Xinhua Liu, PhD

References

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PRINCIPAL INVESTIGATOR:
Prof Jon Ayres

CONTRACTING ORGANIZATION:
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14. ABSTRACT This feasibility study conducted interviews with a small number of males diagnosed as having Parkinson's Disease. A method was devised to interview the participants to assess their previous occupational exposures to manganese and welding work, and to ascertain if such exposed patients differed from non-exposed patients in terms of age of onset and diagnosis. This study has provided two useful research tools and statistical indications of the absence of evidence of risk of Parkinson's disease being caused or accelerated by exposure to welding. We have shown that it would be feasible to conduct the main phase of this study as proposed over a period of a further three years providing sufficient funds were available over and above the previous funding application to allow us to employ at least one full-time Research Assistant. We have shown through the literature review that the knowledge we sought to acquire in the proposed main phase of the study, has been provided satisfactorily by others since this feasibility study started. In consequence of this, no matter how feasible it may be, we cannot now justify an argument for the cost and time required to undertake the previously proposed main phase.					
15. SUBJECT TERMS Manganese, neurotoxicology, iron deficiency, welding, manganese mining, nutrition, Parkinson's disease, movement					
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REPORT OF THE FEASIBILITY PHASE OF A PROPOSED CLINICAL CASE-CONTROL STUDY TO DETERMINE IF EMPLOYMENT AS A WELDER AFFECTS THE AGE OF ONSET OF PARKINSON'S DISEASE

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Introduction

This is the report of the feasibility phase of a proposed epidemiological study to determine if having been employed as a welder affects the age of onset of Parkinson's disease.

Background

Electric arc welding is a ubiquitous metal joining process at the very heart of industry worldwide. Hundreds of thousands of workers in the United States of America and Europe classify it as their principal full-time occupation. Worldwide there may be over a million people employed as welders with three to five million others using welding as part of their occupational tasks. Many other men and women work with and around welders, sharing their working environment. All these workers are at risk of exposure to the fumes and gases which are emitted by arc welding processes. The overall numbers are likely to increase steadily in line with production of steel, the most commonly welded material, as developing countries industrialise. In addition, many others are employed in the large and sophisticated industry researching, developing, manufacturing and supplying welding materials.

Much had been written over the years about the possible adverse effects of welding on health, especially respiratory health, when in 2001 it was reported that there appeared to be a risk of harm to the central nervous system. Those who had conducted a small clinical cross-sectional case-referent study had concluded that employment as a welder was associated with a significantly younger age of onset of typical idiopathic Parkinson's disease than had been found in the control group; 46 years for welders compared with 63 years for those in the control group [1].

Parkinson's disease is a neurological disorder affecting mood and movement. It is a common disease, said to affect one in 500 of the general population and 1% of those over the age of 65. There is no proven causal agent. Studies have suggested that environmental factors, notably exposure to pesticides, may be causally linked to the disease, possibly through interactions with some genetic susceptibility.

The 2001 finding raised the possibility that some exposure resulting from working as a welder caused or accelerated the onset of this disease, provoked debate in legal and occupational health circles, and caused anxiety among welders and in the welding industry. Injury litigation was initiated. Despite uncertainty or ignorance about the bioavailability, transport and effects of compounds present in welding fume, and with a paucity of exposure data or good epidemiology, the putative hazard was identified as manganese compounds in fume from welding steel.

Manganese is an essential trace element for humans. Derived from processed mined ore, its compounds are constituents of several industrial processes. The greatest amount by far is used in steelmaking as it is an essential constituent of all types of steel. In consequence, it is found in particles in the fume emitted from welding steel, that being derived mainly from the vaporisation of consumable electrodes or other filler metal used in the joining process. Evidence from other occupational exposures has shown that excess exposure to manganese and its compounds in dusts and fumes may result in its accumulation in the brain where it is neurotoxic. This may cause the rare mood and movement disorder of "manganism". There is thought to be a sub-clinical form of that disease detectable by neurobehavioural tests.

Manganism and Parkinson's disease are similar but separate disorders with different underlying cellular pathologies. The superficial similarities can lead easily to diagnostic confusion and, in turn, to incorrect assignation of cases in epidemiological studies. The disorders can, however, be distinguished clinically by thorough careful examination and investigation, strict discipline in defining signs and symptoms, then making the correct inferences from the observations backed, if necessary, by special examinations such as MRI and PET scans.

One of the authors of this report (GM) had maintained a special interest in the health of welders and had reviewed related literature since the 1970s. He became increasingly concerned as risk assessments and reports of central nervous system damage occurring in workers said to be welders were promulgated as at least some of the assessments had been developed by possibly inappropriate extrapolation from other work situations and from case reports and epidemiological investigations which appeared to be flawed significantly by imprecision in diagnosis and use of the term "welder". He conducted a systematic review of the literature and concluded that it was impossible to accept or dismiss the contention that employment as a welder, with consequent exposure to manganese compounds in welding fume, enhanced susceptibility to or caused Parkinson's disease in welders and that this matter merited more precise investigation [2].

We came to agree that this further work should include a case-referent study of sufficient power and precision to detect a significant excess incidence of a history of work as a welder joining metal in men diagnosed with Parkinson's disease using defined and strict applied clinical criteria. We set out to conduct this in Birmingham, a city at the heart of industrial England. We resolved that should this excess be found then retrospective assessment of exposure should be attempted to provide a dose-response curve.

As the most challenging aspects of this study would be case definition and selection of appropriate referents it was thought prudent to explore these aspects in a feasibility study before embarking on a large scale investigation. The study aim and design of the feasibility phase were supported by the International Manganese Institute which brought the proposal to the attention of the US Department of Defence, a major employer of workers who weld steel, and USMRMC agreed to fund the feasibility phase, reported here, and, provisionally, the main study.

Aim and objectives

The feasibility phase was designed to define means and determine the feasibility of conducting a definitive case-referent study to determine if there was a significant excess of employment as a welder or in other work with exposure to manganese containing metal fumes in men diagnosed with Parkinson's disease.

The objectives of the feasibility study were to:

1. Develop and use suitable study tools for diagnosis of Parkinson's disease and to elicit a full occupational history within a National Health Service clinic environment.
2. Collect information in the clinic during the development of these tools and seek to use it to test two hypotheses;
 - a. A significantly higher proportion of those diagnosed as having undisputed PD have been welders of steel, or otherwise exposed to manganese-containing fumes.
 - b. Within those diagnosed as having PD, the age of onset is lower among those who have been occupationally exposed to manganese than those who have not.
3. Investigate sources and the process of recruiting sufficient referents suitable to test the hypothesis that the proportion of men in the Parkinson's disease group who have been welders of steel or otherwise exposed to manganese-containing fumes is significantly greater than in the general population i.e. among men in a control group matched for age, family history and other known risk factors but who do not have Parkinson's disease.
4. Maintain a review of the literature to inform the study and, following its completion, assist in determining if there was a persisting knowledge requirement to undertake the main study.

Ethical approval

Ethical approval was obtained from the Solihull NHS Local Research Ethics Committee in August 2007 and USMRMC in October 2007. This was a more time-consuming exercise than we had anticipated but valuable experience was gained in crafting the study design to meet the requirements of each authority.

Methods

Objective 1: Development of research tools

The reliability and validity of the diagnosis of a “case” of Parkinson’s disease is central to the precision of the case–referent study. This diagnosis is not straightforward as there are no biological markers for ante–mortem diagnosis and the decision depends on the presence and progression of clinical features. Misdiagnosis has been shown to be common, particularly in the early stages of the disease. This is a factor which has been suggested as limiting the usefulness of several epidemiological studies investigating the causes of Parkinson’s disease. We decided to overcome this difficulty by applying precisely defined diagnostic criteria in our selection of cases.

A number of sets of diagnostic criteria have been proposed, including presence of at least two “cardinal signs”, Parkinson’s disease Staging Scale and the UK Parkinson’s Disease Society Brain Bank. Drawing on these and other sources we produced a Clinical Record Sheet to be used by two of us (DN & PP) to record the absence or presence of defined Cardinal Features, Supportive Criteria and Exclusion Criteria in patients presenting at their Movement Disorder Clinic on study days. This was completed in the presence of the patient following, rather than during, their usual questioning and examination. This allowed consistency and transparency of allocation of men to the Parkinson’s disease group without interrupting the flow of the consultation.

This Clinical Record also had the potential to provide a record of the clinical history, findings and diagnosis for controls, whether they be the other men who had attended the clinic but were found not to have Parkinson’s disease or a completely separate group. A copy of the Clinical Record Sheet can be found in Appendix 1.

The second research tool developed was the Occupational History Record. This took the form of the template for a structured interview of each subject which could be undertaken by a trained Research Assistant and reduce the costs of a main study. A copy of the Occupational History Record can be found in Appendix 2.

Objective 2: Data collection

In the British National Health Service, Consultants (the senior specialists) in each clinical specialty hold clinics, usually lasting half a day, which are attended by appointment by patients referred by their family general practitioner or perhaps another hospital doctor for diagnosis and/or advice on management or treatment. The study was conducted at the Movement Disorder Clinics (held by DN & PP).

It had been intended that, to ensure that each patient had time to consider their decision to participate, the study would be explained to the patient and their consent obtained at one clinic and the Occupational

History Record interview conducted when they next attended. It was decided by the team that separation of explanation and obtaining consent by a month or more was not sensible and moreover would pose serious practical difficulties. The postal information letter procedure outlined below was substituted.

All males due to attend that clinic were identified each week the study was undertaken and a nominal list prepared on a data base. Access to this and all other study documents was restricted to the four named investigators. An information letter was individualized for each patient by name and appointment date, a clinician member of study team and sent to the patient at his home address. In this the clinician asked the patients to consider taking part in a brief occupational history interview with a psychologist immediately following their next consultant appointment.

Enclosed with it was a further letter, from the chief investigator, setting out details of the study and what would be required of participants, a consent form, and proof of ethical approval. A copy of the Information Letter and Consent Form can be found in Appendices 3 & 4 respectively. Patients were asked to contact the chief investigator or their consultant neurologist with any questions or concerns they had. A contact telephone number was provided and CJ took the calls or responded to voice-mail messages daily. Patients were also requested to bring their consent form with them on the day of their appointment for completion by them and the interviewing psychologist.

At the clinic each patient had a clinical consultation with the consultant neurologist. He completed the study Clinical Record in respect of those he diagnosed as having Parkinson's disease and then discussed the study with the patient, encouraging him to be interviewed by the chief investigator (CJ) and, when practicable, made that introduction.

These interviews were conducted between January and September 2008. They were held in private rooms in the Movement Disorders Clinic. At the outset he checked that the Clinical Record showed that the subject met the prescribed diagnostic criteria then provided the patient with the information already given in the letter sent to their home and responded to questions about this as necessary. The patient, now a potential subject, was shown an example of both data collection sheets and that the top section containing their personal identification details would be cut off and thus physically separated from all the other information which had been recorded. It was then emphasised to them that the risk of a breach of confidentiality would be negligible as confidential information could be linked to them only by the study number, only the chief investigator would hold the list which allowed this to be done and he would prepare that list personally before destroying the cut off top portion of the form. The patient was then asked to sign the consent form to signify having given informed consent for participation.

Using a standardised procedure and the Occupational History Record form as a template, he gathered from the patient details of demography, work history, diet, and lifestyle. If participants confirmed they had

been employed in jobs involving manganese exposures, further questions were asked about such jobs. For welders this would include details such as welding type, ventilation, and exposure details. Data was made anonymous with no personal or identifying details retained, and was stored on a secure and encrypted hard disc, only accessible through password.

Objective 3: Identification of potential controls

Three sources of future controls were explored. The first was those patients who attended that clinic or another specialty clinic and were not found to have Parkinson's disease. The second was to ask each subject at the end of the Occupational History questioning if they would be willing to recruit a male friend of similar age as a control. The third was to seek to recruit the cooperation of the patient's general practitioner to identify another patient who met control criteria to match with our already recruited subject.

Objective 4: Literature review

The literature review initiated prior to the study was continued throughout this feasibility phase and to date. It formed the basis of a paper published in Toxicological Review in 2006 [2].

Statistical analysis

All data obtained from the occupational history questionnaires and the clinical record sheets was entered into SPSS v16 for descriptive and inferential analyses. Analysis of Variance and T-tests were used to make comparison between patients with and without manganese or welding exposures. For categorical comparisons between patient groups, Chi square analysis was made, using Yates's correction for continuity of small samples.

Results

Gaining ethical approval

Delay in gaining ethical approval from USMRMC was engendered by the University not having a current and updated Federal Wide Assurance cover (reference no FWA00008367) which had to be updated by the University. This was eventually re-established and was put in place until renewal would be required again by 30th May 2010.

An additional delay was incurred by the University not having current and updated OHRP Human Subjects Assurance Training certificates for each of the investigators in the study – as this is not standard requirement of researchers in the UK. This was established for each member of the research team as soon as possible.

Provision of information and obtaining consent

All patients attending for interview were found to have received the invitation and information letter sent to their home. In most cases there proved to be a need to revisit the explanation to be confident that they understood the study objectives and methods, and were thus equipped to make an informed decision about participating. All subjects interviewed were content with arrangements for the study, including those to safeguard the confidentiality of information, and gave their informed consent.

Data collection tools

The clinicians found the Clinical Record sheet proved to be easy to use in a clinical setting to provide a permanent record of the presence or absence of pre-defined diagnostic features of Parkinson's disease. They considered that completing it did not add significantly to the duration of the consultation.

It also allowed the clinical findings to be compared to the diagnostic criteria set for the study (defined on the form as an aide memoir) and thus identify the patients with confirmed Parkinson's disease. The Occupational History interviewer did not need any clinical knowledge to check that the patient sent to him satisfied the diagnostic criteria. He needed only to check that the *number* of features marked as present met the numerical criteria for that section of the form.

The Occupational History Record proved to be a useful template to ensure disciplined and thus consistent structure for the interview and to guide the questioning to cover all possible exposures relevant to the interviewee, ensuring a comprehensive occupational history. Interviews lasted between 5 and 20 minutes, depending on the answers given by participants. There was noteworthy advantage in having the man's wife in attendance as, although the interview took longer, the women proved to have better memories than their husbands and provided much additional useful information about their

employment. The standardised structure of the Occupational Health Record appeared to be suitable for use by a trained Research Assistant without a clinical background.

Data analysis

Fifteen patients with confirmed Parkinson's disease were identified using the Clinical Record. Three records were destroyed in a domestic accident before they could be added to the database. Thus 12 records were available for analysis.

The mean age of participants was 70 years \pm 10.8, with the youngest being 50 and the oldest being 85. The mean age upon diagnosis of PD for the participants was 62.9 years \pm 13.7, with the youngest being 37 and the oldest being 78. At the point of interview, the mean time elapsed since diagnosis was made was 7.4 years \pm 9.2, with the shortest time being 1 year and the longest time being 31 years.

The first hypothesis to be tested using this limited data set was that a significantly higher proportion of those patients diagnosed as having undisputed Parkinson's disease had been welders of steel, or otherwise exposed to manganese-containing fumes. It was found that none of the men with the disease had worked as welders, although 2 (16%) had worked in jobs involving some occasional welding; one as an apprentice engineer with some welding work for 4 years and the other as a central lathe turner with occasional welding for 50 years. A third participant had worked as a car mechanic for 44 years and divulged that he frequently worked in the presence of colleagues who welded. These three participants who confirmed they had workplace welding exposures had a mean exposure period of 32.6 years \pm 25.

The second hypothesis to be tested was that within those diagnosed as having Parkinson's disease the age of onset is lower among those who have been occupationally exposed to manganese. Inferential analysis showed that the mean age of Parkinson's disease diagnosis for welding-exposed participants (n=3) was 64 years \pm 14.5, compared with 62.5 years \pm 14.3 for non welding-exposed participants (n=9), although this was not significantly different (F=0.02, P=0.88). The mean years elapsed since Parkinson's disease was diagnosed was 2.3 years \pm 1.5 for the three welding-exposed participants compared with 9.1 years \pm 10.1 for the nine non-welding-exposed participants (n=9). This difference is not statistically significant different (F=1.23, P=0.29).

This analysis was repeated in respect of the two men who had worked as welders. The mean age of PD diagnosis for them was 63.5 years \pm 20.5 compared with 62.8 years \pm 13.5 for those ten men who had not been welders. The difference in age of diagnosis is not significantly different (F=0.00, P=0.95). The mean years elapsed since PD diagnosis for participants who worked as welders was 1.5 years \pm 0.7, compared with 8.6 years \pm 9.7 for the others. Again, this difference is not significantly different (F=0.98, P=0.34).

Selection of controls

All participants said that they would be willing to try to recruit a friend of a similar age to act as a control. It was observed that a substantial number of men referred to the clinic were not diagnosed as having Parkinson's disease.

Literature review

Three well-designed and implemented studies of employment as a welder being a risk factor for Parkinson's disease published since we embarked on our investigation have been identified in the literature. The earliest of these, published in 2007, identified 767 cases of the disease in five European countries [3]. A standard definition was used. No association suggestive of a causative role was reported with regard to exposure to copper, iron or manganese exposure. In 2009 Stampfer reported on a study examining mortality from Parkinson's disease and other neurodegenerative diseases in 107,773 men in the United States who had had welding-related occupations [4]. After sophisticated analysis (adjusting for attained age, race, place of residence and year of death) the data did not support an association between welding occupations and death from Parkinson's disease or other neurodegenerative disease, nor that welders are at increased risk of dying from Parkinson's disease at a younger age. Also in 2009, Tanner and colleagues reported on their case-control study of the risk of Parkinsonism in occupations including welding, specific job tasks and toxicant exposures putatively associated with parkinsonism [5]. This was conducted in eight movement disorder centres in North America. Having analysed findings in 519 cases and 511 controls they found that welding was not associated with increased risk of Parkinsonism or with younger age at diagnosis.

Discussion

During this study we have developed two research tools and gained experience in arranging ethical approval to meet the needs of authorities in UK and USA. It has proved that the methods we have devised would make it be feasible for us to recruit subjects and use National Health Service clinics and the two research tools to conduct an epidemiologically sound, ethically approved study of the incidence and age of onset of confirmed cases of Parkinson's disease among those with a history of work of occupational exposure or no occupational exposure to welding fumes.

The small number of Occupational History interview records completed was sufficient to test our methods and identify how these should be improved by ensuring the availability of an interviewer at all the clinic sessions; this had not been possible during this study. In a main study we would employ and train a Research Assistant to attend every Movement Disorder Clinic held by the clinicians in the team, organise patient attendance, provide information and obtain consent, and conduct the structured interview to obtain the Occupational History. Whereas sufficient cases were studied to test our methods there were too few to test the hypotheses rigorously. That, however, is the primary task for the main study should this be done. Analysis of data from the 12 attendees did not support the hypothesis that there is a causal association between work as a welder or exposure to welding fumes and the development of Parkinson's disease prematurely or at all. Selection of controls for a large study will prove challenging. We had considered asking the general practitioner of each patient with confirmed Parkinson's disease to match him with another of his patients and invite him to permit his contact details to be provided to the study team. This method would have to be covered by an umbrella ethical approval - which should not present a problem. We have been advised, however, that we would be expected to cover the GP's costs and that these might prove to be appreciable. It would also make the study's administration more labour intensive. Having considered these factors we have chosen not to include that method in the design of the main study. We are attracted to recruiting as controls the patients attending the Movement Disorder Clinic who are not found to have Parkinson's disease and secondly patients attending a hospital clinic for a condition which is not neurological. This would be entirely feasible.

Moving to the literature review, we embarked on this study because, while no convincing evidence to support the hypothesis that either exposure to manganese or employment as a welder causes or is a risk factor for causation of Parkinson's disease had emerged from a large body of epidemiologic and clinico-pathological investigations of widely varying quality, we could not easily dismiss welding fume as a possible risk factor which might facilitate the onset of the disease.² As reported above, that is no longer the situation as we have identified in the literature review three sound studies where investigators have sought and failed to find evidence to support the contentions that welding is a causal factor for Parkinson's disease or of its premature onset.

Conclusions

We conclude that:

- This study has provided two useful research tools and statistical indications of the absence of evidence of risk of Parkinson's disease being caused or accelerated by exposure to welding.
- We have shown that it would be feasible to conduct the main phase of this study as proposed over a period of a further three years providing sufficient funds were available over and above the previous funding application to allow us to employ at least one full-time Research Assistant.
- We have shown through the literature review that the knowledge we sought to acquire in the proposed main phase of the study, has been provided satisfactorily by others since this feasibility study started. In consequence of this, no matter how feasible it may be, we cannot now justify the cost and time required to undertake the previously proposed main phase.

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Appendices

- Appendix 1** Clinical Data Sheet

- Appendix 1** Occupational History Questionnaire (talked-through version)

- Appendix 1** Patient Information Sheet accompanying their appointment letter

- Appendix 1** Consent Form



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Parkinson's Disease & Manganese Project Occupational History Interview

Private and Confidential

For Medical Research Only

Dr Grant McMillan
Honorary Clinical Senior Lecturer
Institute of Occupational and Environmental Medicine
University of Birmingham

Dr C.A. Jackson
Honorary Senior Lecturer in Occupational Psychology
Institute of Occupational and Environmental Medicine
University of Birmingham

February 2006

A. Date of Birth _____ / _____ / _____

B. Sex *Male / Female*

C. Have you ever been employed in any of the following occupations or worked in any factory concerned with these jobs or processes?

- | | |
|---------------------------------------------------|----------|
| 1. The manufacture of rubber and rubber products | Yes / No |
| 2. Cable manufacturing | Yes / No |
| 3. The manufacture of dyes and dyestuffs | Yes / No |
| 4. Manufacture and professional use of solvents | Yes / No |
| 5. Leather work | Yes / No |
| 6. Welding of metals | Yes / No |
| 7. Manufacture or professional use of paints | Yes / No |
| 8. Gasworks and coke ovens | Yes / No |
| 9. Rodent or pest extermination | Yes / No |
| 10. Sewage works | Yes / No |
| 11. Laboratory technician | Yes / No |
| 12. Medicine or Nursing | Yes / No |
| 13. Textile printing and dyeing | Yes / No |
| 14. Manufacture of plastics | Yes / No |
| 15. Hairdressing or Beauty therapy | Yes / No |
| 16. Metal casting | Yes / No |
| 17. Printing | Yes / No |
| 18. Metal smelting | Yes / No |
| 19. Professional use or manufacture of pesticides | Yes / No |

D. Please give details if you have answered "Yes" to any part of "C". Give the name of the firm, describe the work you carried out and give the years you worked.

DATES

NAME OF FIRM	JOB TITLE	JOB DESCRIPTION	FROM	TO
.....
.....
.....

E. We are interested in any metal welding work you may have done.

1. What was your job title? _____

2. How many hours a week were you working as a welder? _____

3. How many years in total did you work as a welder for? _____

4. What type of metal were you welding?

Stainless Steel (____ %) *Mild Steel* (____ %) *Other* (____ %)

5. Can you remember what type of electrode you used most? _____

6. What type of welding technique did you use?

Manual Metal Arc (MMA) (____ %)

Tungsten Inert Gas (TIG) (____ %)

Metal Inert Gas (MIG) (____ %)

7. What kind of engineering control was used?

General Ventilation (____ %)

Local Exhaust Ventilation (LEV) (____ %)

Only Natural Ventilation (____ %)

8. If LEV was used, how far was the hood from the welding area? _____

9. Did you wear a welding visor when welding? Yes (____ %) No

10. What immediate surroundings were you in mostly when welding?

Indoor (____ %)

Outdoor (____ %)

Enclosed space (e.g. inside a tank) (____ %)

11. When welding, were you near other welders? Yes (____ %) No

12. Over an average 8-hour shift, how much time did you spending arcing ____ *hrs*

F. We are interested in your diet and smoking habits

1. Have you ever smoked cigarettes regularly (at least once a week)? Yes / No

2. Which year did you start smoking regularly? _____

3. Number smoked per day
Less than 10/day 10-20/day More than 20/day

4. Which year did you stop smoking regularly? _____

5. How many years have you smoked for? _____

6. Which of the following have you eaten regularly (at least once a week)?
Spinach Lentils Liver Poultry
Whole grains Cereals Red meat

7. Do you currently take daily vitamin supplements? Yes / No

8. Which vitamins? _____

9. When did you start taking daily vitamins? _____

10. Have you ever taken any of the following substances?
"Angel dust" "Ozone" "Wack" "Rocket fuel"
"Killer joints" "Crystal supergrass" PCP Phencyclidine

G. Finally, we would ask for some extra information about you.

1. What is your marital status? _____

2. How many children do you have? _____

3. What is the highest education achievement you have made?
School-leaving exams O-levels A-levels Diplomas
University degree Certificates Post graduate degree

Thank you for your time and cooperation



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Parkinson's Disease & Manganese Project

Information Sheet

Dear Sir

As you are being offered an appointment at the Movement Disorders Clinic in the Department of Neurology at Queen Elizabeth Hospital Birmingham, we are passing this information sheet to you to ask you to consider taking part in a small study concerning the development of Parkinson's Disease. We are approaching everyone who is offered an appointment in the department, so please do not feel you have been "singled out". We wish to investigate the possible link between Parkinson's Disease and some occupations, especially jobs involving welding work. We hope to publish the results of this study in a medical journal for other health professionals to read – your personal details will never be disclosed.

We would like to invite you to speak to one of our research team for 10-15 minutes when you are in the department for your next appointment. This would be for a brief and confidential interview in a private room where we would like to ask you some questions about any jobs you may have had in the past. That is all that will be required of you, and you will not be approached again for any other details. In your appointment, your neurologist will perform three brief clinical evaluations of your movements – which will take only a few moments. Everything will be kept confidential, and we will not even need to know your name. **We are interested in hearing about any occupations, but we are especially interested in speaking to people who have worked as welders of metal.** Even if you have not "worked" as a welder, but have done some welding work in the past, we would still be keen to hear from you.

It is important for you to know that taking part is entirely voluntary and if you decide not to take part, your appointment and treatment will not be altered in any way. If you do not wish to take part, you need do nothing further and we will not trouble you again.

If you feel that you would like to take part in this research study, please return the consent form that is printed on the reverse of this letter, and return it to the address provided on the freepost envelope. If you would like to speak to the research team with any questions you may have, please feel free to call on **0121 331 5338** and the lead researcher will be happy to speak to you.

Yours faithfully

Dr Craig. A. Jackson BSc MSc PhD C.Psych
Honorary Senior Lecturer in Occupational Psychology
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Parkinson's Disease & Manganese Project

Consent Form

Please read below and tick the necessary boxes if you wish to participate in the study

“I confirm that I have read and understood the participant information sheet for this study, and I have had the opportunity to ask questions.”

“I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical and legal rights being affected.”

“I agree to take part in the above study.”

Name of participant

Date

Signature

Name of researcher

Date

Signature

1 copy for participant
1 copy for researcher
1 copy for hospital notes