A CASE OF PIRIMIPHOS METHYL POISONING

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The following case is interpolated into my paper 'Sensitisation : clue to the pathology pathway of chronic organophosphate poisoning. A review with case reports' (March 1999).
Most review bodies have concentrated on examining the claim of long term poisoning by OP sheep dips, and ignore pathology pathways. Here I present a case of long term low level exposure to pirimiphos methyl and an analysis of the abnormal acetylcholine (ACh) transmission induced. Pirimiphos methyl is considered a safe insecticide. It is used under the trade name Actellic to protect stored grain from infestation. It remains concentrated in the husk and is thus incorporated into the human and farm animal food chain. The manufacturers - Zeneca - maintain that its low toxicity makes it safe for the consumer and safe also for the operator treating the grain. This claim is supported by MAFF's Advisory Committee on Pesticides (ACP). The effects of long term low level exposure have never been examined.

11. An experience with a safe insecticide

Pirimiphos methyl, an organophosphate marketed as 'Actellic' is used to treat grain in store against mite and insect infestation. Its current formulations are 'Actellic 2% Dust' in powder form, 'Actellic D' containing solvents and diluted for spraying and 'Actellic' smoke bomb generator for treating surfaces. Actellic 2% Dust was introduced in the mid-seventies by ICI and is now marketed by Zeneca, formed after an ICI demerger in 1993. The Product Safety Data 1994 (para 15) stated it was 'Not classified as hazardous to users' and 'Do not breathe dust. If necessary, for personal comfort wear a mask.' The Product Use Manual 1998/99 [75] states that 'under normal conditions of handling and use... it is of low toxicity, inhalation is unlikely to cause harmful effects, and in long term exposure, no long term risks to man are associated with it. ' It further advises -

Treating grain: protective clothing consisting in 'gloves made of nitrile, butyl rubber or PVC materials preferably in gauntlet fonn. Face mask to BS2091/ENl40 plus filter to EN143P2SL to protect against dust.' Wellingtons are not mentioned.

(Note that the ICI Product Safety Data as late as 1992 only advises protective clothing in cases of 'accidental spillage' (para 6): 'This means wearing a face mask that gives protection against toxic dusts, eye protection, chemically resistant gloves, boots and coveralls.' The difference between exposure to a spillage and exposure while treating grain (controlled spillage?) is unclear. It would be useful to obtain earlier Product Safety leaflets).

Handling the treated grain 'does not require the use of face and eye protection. However dust from the grain itself has been known to cause irritation of eyes, throat, chest and skin and so when working with grain the use of eye protection and a face mask is advisable.'

There is no legal requirement for the operator to have a certificate of competence to treat stored grain with pirimiphos methyl. This follows because treatment with an OP for food storage is believed to pose no threat to the operator, the environment or the human or animal consumer.

1997 the Advisory Committee on Pesticides evaluated pirimiphos methyl for the Pesticide Safety Directorate (PSD) [76] and on the basis of acute and chronic toxicity studies in animals fed various dietary levels 'considered it was of low acute oral and dermal toxicity.. The human data is extremely thin. (i) Since 'the toxicological database indicated that cholinesterase inhibition was the most crucial end point and human volunteer studies were available which adequately investigated this end point, it was considered reasonable to base the derivation of the acceptable daily intake (ADI) on two human volunteer ingestion studies with a no observed adverse effect level (NOAEL) of 0.25 mg/kg bw/day for 28 and 56 days,' Supported also by long term animal studies and with an additional safety factor of 10,. it was proposed that the ADI should be 0.03mg/kg bw/day (until 1992 the ADI had been 0.01mg/kg bw/d[p89]. (ii) The only operator exposure studies quoted were two 3 day studies of human volunteers treating stored grain and spraying houses against mosquitoes, with no clinical manifestations of exposure and recovery of depressed acetyl cholinesterase activities after 24 hours. There were no notable differences between workers wearing normal and protective clothing. Hence it was proposed that the

admissible operator exposure level (AOEL) should also be 0.03mg/kg bw/d [p 110-111]. (iii) The total number of adverse reactions from exposure to pirimiphos methyl reported to the manufacturer 1985-1994 was 165 (56 for Actellic). Symptoms reported for Actellic dust included nausea, headaches, vomiting, irritated/sore skin and face, lethargy. The company stated that the incidents could have been avoided with better working practices. The PSD recommended that approval for all uses should continue.
No long term studies of exposure have ever been made. Post surveillance, as with all licenced chemical products, depends on reports of 'incidents' correlating with exposure. Hence cumulative effects while acknowledged [77] have never been investigated and sensitisation is dismissed as a psychiatric problem.

John Coyte farms 400 acres and grows some 250 acres of grain which he sells to merchants as milling wheat and malting barley and for feed wheat and barley. keeping back what he needs for his own cattle. Grain brought in off the field and during the drying process is of a humidity that allows mites and insects to breed in it and this is prevented by pirimiphos methyl treatment. Any trace of mite or insect and merchants will not accept it. John has applied Actellic 2% dust (20g/kg) since it was introduced in 1976/77. He scoops it out of the bag with a measuring tin and works it into the grain with a shovel at 45g/m^2 (200g/tonne). The Product Use Manual states this gives an occupational exposure limit of 3mg/m^3. It warns that all contact with skin must be avoided and clothing contaminated with the dust washed before re-use.
After the application his only contact with Actellic is via the treated grain. This must be checked frequently for moisture content and weevils during storage, moved if it overheats and transferred to lorries by front-end loader once it is dry enough to send away. But that is not the end. For years he handled it on a daily basis, rolling it for his cattle and mixing it with other ingredients in their feed.

Now 56, since leaving school at 16½. he worked hard at building up the family farm" The dozen cows he was milking in 1958 became 90 cows at one stage and the arable acreage was increased. He was never ill. Neighbours recall: "1985 you were so fit you could jump over a five barred gate....You were without doubt the fittest man in the area."
In the early nineties he began to suffer muscle spasms, then deteriorated rapidly, overcome by physical weakness, headaches, exhaustion. irritability and anxiety. It was worse at harvest time:
he was agitated and worried about everything. There is no reason why he, an experienced farmer should have become agitated at harvest, but as the grain came off the combine into store he would be treating it with Actellic. He could not understand what was happening to him. Summer/autumn 1995 he was 'so ill I could not stand up'. He had 'fits of shaking....horrendous headaches....' He was 'too weak to open the gate to let the cows in.' A business colleague later told him "When I saw you, you did not know who I was ...you were very rough with no inclination to move from the sofa...we could not conduct business that day."

John Coyte keeps a diary where he records his activities, and he began to note down every detail of his symptoms. There was endless sweating, but cold feet. He could not hold his watel: and at other times could not pass it. He had diarrhoea. A..rash on his legs. ('the grain gets into your shoes'). He was disorientated. Short term memory was impaired. He had hallucinations, anxiety over trivia, bouts of irritability and depression. His near sight began to go. No one knew the cause of it. He was in despair. Under pressure he agreed to attend a behavioural clinic. They found nothing wrong and dismissed his suggestion of OP poisoning. Doctors were unhelpful. One of them told him 'there is nothing the matter with you. OPs are an imaginary thing.'
He had pain in his right foot and was told it was gout. He developed a cough and was told it was farmer's lung. Then he noticed that his three year old son who used to accompany him to roll the grain had the same awful cough and was diagnosed stage 2 asthma. He contacted the National Asthma Research and Respiratory Training Centre at Warwick and suggested that asthma could be a symptom of OP poisoning. This they denied. But when his wife left him in 1995 and the little boy was no longer exposed to the treated grain, the asthma cleared.

1995 he could no longer manage milking and November 3rd he sold his dairy cows and changed to sucklers. It meant growing about 50 acres more grain, but he felt better after stopping milking: 'I was not having the daily top-up from rolling corn.'

His breathing difficulty suggested a heart problem but at Derriford hospital, Plymouth they found

his ECG was normal. 1996 the GP referred him to a neurologist about the muscle spasms in his arms and legs, the pain in his feet and a loss of use of his right foot. He took in an empty bag of Actellic and asked for a medical opinion as to whether he should continue using it. He was sent home with the empty bag, no advice and no treatment. There was no one to turn to. He felt isolated. Medical practitioners suggested it was all in the mind. Family and neighbours thought he was a crank: 'putting my life through hell in ignorance.'

His balance was poor. 1996 on a family outing to a fair he took his two children on a kiddies' roundabout and kept falling off. It affected him so badly he had to be held up and was too sick to drive the car. April 1998 a second neurologist diagnosed peripheral neuropathy during a survey at Derriford. Nothing came of it and he was not informed of the result until July 21st after his first collapse.

No one medically told him not to use OPs although he repeatedly suggested that might be the problem. He refused to spray his crops with them and when MAFF 1997/98 conducted a 4 year trial on his farm to study the effects of sublethal doses of demethoate on pest predators he insisted they sprayed it themselves. The prominent OP campaigner Joanna Wheatley warned him,against Actellic as did fellow farmers Shirley Bray and Richard Bruce: Mrs. Bray and her husband were made OP victims in the early eighties and Richard Bruce had been disabled by Actellic poisoning in 1992. Could they be right? he argued that he was already wearing more than the necessary protective gear. He did not want to be labelled a hypochondriac. Pirimiphos methyl was going into the food chain. Surely he told himself, it must be safe.

Spring 1998 he moved the winter barley into the main grain shed. 150 tons, it had been treated in November with Actellic at 7oz/ton. Later it was loaded into lorries, a ton at a time.
May 30 in full safety gear he surface-treated some grain with a small amount of Actellic. June-July symptoms were severe. 'June 5 Downstairs at 3.30am for ibobrufen. June 10 Fatigue. Right arm muscle locked. June 11 Went to sleep 3 times in day. June 12 Cold feet. Sweating. Eyes running. June 16 Very weak end of day. Barely put one foot in front of the other as I walked through yard gate. Shaking. Pain. Muscle spasms. June 22 Good day. Very little pain. Fingers and hand locked for several minutes. Couldn't pull them apart. June 23 75% pain right leg 25% left leg. June 24 Took children to church. June 30 Saw doctor about weakness in right hand. Legs shaking.Very weak. Fri 4 July No further pain... just bitter taste in mouth and confusion. Can't work out any problems. OP headache all day... Stomach cramp. Sweating. Feet stone cold. Eyes running. Legs shaking. I am sure the symptoms are the same as Mum had.'

In the early eighties his mother had collapsed. She lost her memory and changed her behaviour. Shouted and banged on the table. She could not dress herself or tell one shoe from the other. She went back into a shop to buy bread after she had just bought some. She walked in front of a car and asked uncomprehendingly 'why did he blow his horn at me?' She was then in her sixties. It was she who had washed his clothes by hand, including his waterproof overalls, washing them in the granite trough in the back kitchen. Alzeimers was diagnosed. John said: 'She suffered terribly.' He looked after her for 18 years, except during his five years of marriage, when she lived with his sister and brother in law.

His first collapse was July 20 1998. He had treated his grain wearing full safety gear at 10.00 am the day before. Next morning he had nausea and a tight painful chest He rang for emergency help. When the ambulance came he was found lying on the lawn, conscious but immobile except for his eyelids twitching and his teeth faintly chattering. He was revived in the ambulance with oxygen. At Derriford, walking down the hospital passages he was disorientated, going in the opposite direction to the way he was told. He asked if there was anyone experienced in potential OP poisoning. No notice was taken: to the hospital his tight chest and difficult breathing suggested heart disease. The ECG was normal. His pulse, normally low at about 50 beats/min was racing at 100. He was prescribed the *B*-blocker atenolol for high blood pressure. A blood sample was taken and he was discharged at 4.30 pm, but on phoning back to check they were" going to test for red cell and plasma cholinesterase, he was told 'it was not necessary', and 'they were not obliged to test for it' It was not until July 2nd 1999 that he learnt they did in fact comply with his request and was shown the Medical Toxicology Laboratory (London) report where the analyst;had written: “changes in blood levels from low level exposure. would be difficult to evaluate one way or another.” Across this careful assessment his GP had written 'Normal'.

July 21st, the day after his collapse he records: 6.15am Nausea very weak right hand...usual right leg problems. 7.30 Chest tight. Shakes. Lie on settee...a bit better. 8.40 Saw GP to review collapse...took him in urine sample for metabolites (the sample was never analysed).....shaking...memory loss...chest tight..couldn't lay table...OP headache all day.

Despite feeling so sick he was determined to get tested for his cholinesterase levels. He contacted Dr. Sherwood Jones of the Health and Safety Executive (HSE) in Nottingham who advised that the local office would take a blood sample. The local office refused. Dr. Jones intervened and the local office told him he could come in. He drove as far as the outskirts and too sick to go further, a friend took into the Plymouth USE office where a blood sample was taken and a urine sample for metabolites.

Aug 13 A second blood sample was taken for comparison. Despite repeated requests he did not receive the results of the first test until Nov. 17 where it was reported: “the cholinesterase measurements are not conclusive either way in defining whether excessive OP exposure occurred, although the specific activity measurements suggest that some OP absorption had taken place (0.327 kU/mg protein, which is below the lower limit of normal reference range of 0.395 kU/mg protein for plasma cholinesterase). To. prove cholinesterase inhibition you really need a base-line which we don't have.. He was only shown the report of of the second test July 2. 99, again inconclusive. He was as will be seen, still being exposed to Actellic.

Meantime that same day after his collapse the GP had phoned the Pesticide Incidents Appraisal Panel (PIAP) for advice and learnt that if his patient had seven recognised symptoms of OP poisoning then he must have it. From then on his GP was understanding and helpful. Derriford too were now saying he should keep away from OPs. This he had already resolved. .

For the next few days his diary was almost unreadable. Beside misspelling his writing was a jumbled scrawl because he was 'too weak to push the pen.' 'July 22 lbobrufen....pain....losing account of time... same symptoms as summer 95 when collapsed ...Rib cage went rigid...sweating but stone cold...couldn't remember (brother-in-law's) telephone number...cattle movement book Couldn't spell ...(brother in law) put cattle through sale room. I stood there by rostrum but blank. July 24 Awoke 4 am memory loss...rang (brother in law) 4.50am re collecting children, worried I'd get the time wrong...I'm sure these symptoms are the same as mum had...no further pain...just bitter taste in mouth...can't work out any problems. July 25 Better memory...eyes running...this week now seems blank...difficult to open a can of beans ...hands weak ...can't think straight....Possible exposure 1995? July 26 Ran bath for mum...pulse 58..memory much better

July 27 Feeling more calm. No wind, so went Burntree field to spray docks. Just a bit to do. Read directions. Only mecaprop dicamba (a chlorinated hydrocarbon)...non..0P. Started spraying with only ⅓ tank left. Felt breathing difficulties and shaking. Got off tractor. Took off breathing mask to get air. After treating two acres I could barely get back to the farm. Drove tractor as hard as I could... worried I wouldn't make that mile and a half back home. Freezing cold...pulse 80, up from 48. Tried to phone emergency. No answer. Better late morning...phoned firm's toxicologist..said it was OK to use mecoprop...Was it the OP residues still on the mask or was it mecoprop?

July 28 Slept OK. Memory better. Still feeling pretty flat Have only wanted to operate in a very defined area..A distaste for all drinks except tea and water. Distaste for bright lights, including reflections on cars.

July 31 Best morning since sprayed docks. Aug 3 Right leg from knee to backside muscle pain. Aug 4 4.30am Feeling much better..,not so confused...breathing seems normal...pulse 48. Aug 6 Best morning I can remember... only right hand and right foot pain seems permanent' He could read the diary easily, his hand-writing better now he could put pressure on the pen

Aug 8 was his second collapse. 7.00am 'Possible minute exposure in machinery shed' when getting out his tractor to do some baling. The machinery shed was next to the grain store. By 10am his legs were weak, with little feeling. He was shaking. Pulse creeping up to 100. 1.40pm he rang for help and the ambulance came 2.30. He was found on the couch gasping for breath, unable to speak, and given oxygen. By 3.15 when a Derriford doctor arrived he was recovering. His pulse was over 100. This doctor seemed to understand OP poisoning but said atropine was not necessary. He increased the prescription for atenolol to 100mg to bring down his blood pressure (halved by his GP on the Ilth).

John turned to Richard Bruce for advice. Richard explained that if the store adjoined the

machinery shed the dust would get in the shed. There would be grain residues in the machinery. Richard could not tolerate even minimal exposure and it was clear that now neither could he. Next day, just to get the tractor out of the shed he 'dressed up in blue overalls, a PVC suit, wellies, gauntlet gloves and face mask.'

Aug 10 Pulse 45. Aug 11 'Everything went numb... right arm from hand to elbow and right foot to backend went numb.' It happened when he was driving and he went straight to the surgeiy where he lay across two chairs in the waiting room until taken to Derriford by ambulance as an in-patient, this time with a note from the head of the practice drawing attention to OP poisoning. At Derriford he was reported as having great difficulty in expressing himself. Pulse 52. One doctor told him he had 'all the symptoms of chronic OP .'

Aug 12 On the farm there was barley to be loaded which he would have to supervise. He was asked to come back for further tests but heard no more. 11.30pm 'went to bed shaking all over. Think I didn't go near grain shed where the grain was being loaded.'

Aug 17 'Fatigue...slept on settee.' Aug 19 his GP took a blood sample to check his cholinesterase levels. It was sent to a laboratory in Leeds that later reported the cholinesterase activities were in the lower half of the reference range.

Aug 22 3am 'In kitchen.. nausea... 7am nausea... stomach pain. Aug 23 Feeling better. Went for shaft (in car).

Aug 24 was his third collapse. 4.00am ' Feeling better...pulse 52 went to get parts (in car)...came back...breathing difficulty.' He rang for help and was taken to Derriford by ambulance, given oxygen and put in intensive care. 'Pulse 113. Chest very tight..severe headache and pain in back of neck. Derriford did two ECGs, convinced it was his heart. Both normal.' His GP 'offered him all sorts of potions' which he refused.

He recalls "There was a time in August which is almost blank. I didn't know where I was. I was looking at my sucklers and didn't know what I saw. I couldn't layout two knives, two forks and two spoons for my mother and I at breakfast. I couldn't write. Couldn't spell. Speech got slurred and very quiet. I was disorientated." A friend wrote: 'His speech is very slow...the depth and clarity of his thinking very muddled.' It is not clear when this was. Sometimes he felt too ill to write his diary.

Oct. 21 The roller door of the grain shed had opened after a gale. He did not go inside to examine the wheat He just pulled down the door. One hour later on a visit to his neighbours' farm to see their bull, he had breathing difficulties and his hands and feet were shaking.

There were two episodes of amnesia when out on his tractor. Two days close together in October, about 5.30pm when he was tired. The first time he records going on his tractor to Above Town field where he had cut back diagonally across. Couldn't remember where he was. Hard to find the gate. The second time he was going on the tractor to see the mechanic. Never got there. He found a place to turn round and come home because he could not remember where he was.

He searched for someone to explain why he had had the third collapse '36 days after the event' ie. after treating the grain with Actellic Dust July 19. He had already received advice from Dr. Timothy Marrs, Senior Medical Officer at the Dept of Health and leading OP toxicologist who before his first collapse assured him every medical practitioner had recently been issued with a copy of 'Proudfoot 2' with notes for guidance in pesticide poisoning. including advice on the chronic neuro-behavioural effects of OPs. He now went to London to see him. Dr. Marrs was 'helpful and kind' and suggested his second and third collapses were due to 'late arryhthmias.'

Dec.14 He was invited to be interviewed in London by COT's Working Group on Organophosphates. They seemed to him to be concerned. He told them pirimiphos methyl went into the food chain and this appeared to worry at least one of them. They asked questions about his use of pirimiphos methyl. He objected that the term 'use' was imprecise. 'Using it' once to treat grain was not the same as being continuously exposed to it. He explained he had to inspect it for moisture and weevils once a week. spearing out a sample. This year in addition, because he couldn't sell it in the Autmn 97 when the market collapsed, he had to move 150 tons of barley from one store to another in the spring, a ton at a time on his front end loader, and then again load it all up into lorries, each time with the dust from treated grain

flying around. They thanked him for the practical picture he had given them.
Dr. David Ray at the Medical Research Council (MRC) Toxicology Unit, Leicester had written 'How safe are organophosphorous pesticides?' for Pesticide Outlook [78] maintaining 'there was no convincing evidence for low level exposure effects.' He phoned Dr. Ray and challenged his psychiatric interpretation of OP victims' problems. He told him of the difficulties put in his way when he wanted his cholinesterase levels tested. It was a long call. Dr. Ray was sympathetic. He first suggested John's breathing problems were due to farmers' lung, contracted from the dust of the grain itself. but the spasms, pain, shaking and other symptoms forced him to concede OP poisoning: 'although he wouldn't have thought it long term low level. He'd have thought it was acute exposure.'

Slowly John's symptoms have abated, although 'I'm left with permanent damage.' He still gets very tired: May 31 99 'Tried to get out this afternoon and pull a few wild oats and had to go back to car to sleep was alright this morning...a lot of spraying going on around us.' All chemical triggers must be avoided or the shaking and breathing difficulty returns - Sense of smell is dulled but paints and perfumes are overwhelming.' The muscle spasms of 12 months ago have largely gone.His respiratory problems are much reduced - their quick recovery due he thinks to the fact he never smoked. His writing and speech are improved. His memory lapses not so severe. His forehead used to be dead. There is some life in it now, but he gets tingling in the left side of his face as far down as the cheek and a nerve 'jumps on top of my head.' Bumping about on the tractor can make him light headed and nauseous. His long sight is not too bad but near sight is a blur. His teeth are beginning to crumble. The pulse has risen to a steady 60 and after 11 months he stopped atenolol. The only drugs he ever took were atenolol for high blood pressure and paracetamol and ibobrufen for pain. He always refused prozack and other psychiatric drugs because "I learnt to cope with my symptoms. I relied on my strong faith."
Despite farming and financial worries he is more relaxed. The most distressing physical symptoms are the loss of feeling in his right foot, and the excruciating pain that comes and goes in his right heel, calf muscle, knee and backside. Because he cannot feel where his foot is, he cannot gauge anything, especially on rough ground, so sometimes falls over. The most distressing mental symptom is an inability to think clearly and work things out. When his cattle were TB tested in May and he got two groups muddled as to which lot had been done, it was this that wound him up. The fact that one of the cattle proved to be a reactor (putting a restricted movement order on the farm) did not worry him.

There has been 'a dramatic change in Derriford in the last 6 months.' In the spring there was an OP conference. He was referred to a neuropsychologist for cognitive tests, where he reports he is not doing well. It takes him three times as long as it should to do them 'Could not think of more than 4 words beginning with 's' in one minute.' Dr. Copstick is helpful and efficient. She referred him to consultant psychiatrist Dr. D.R.Davies, who has had many chronic OP victims particularly in the SW of England referred to him.

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His mother goes to a day centre. The day centre staff were worried that she had been misdiagnosed. She was very much improved and answered questions she could not have answered if she had Alzeimers nor, they argued would she still be living 18 years after the diagnosis. They sought the assistance of the visiting psychiatrist, Dr. Michael Price. Dr. Price gave her a SPECT scan and called John in to give him his mother's history. The SPECt scan had showed frontal lobe syndrome: hyperperfusion of the left and right frontal lobes. She did not have Alzeimers. John learnt from sheep-dip victim and campaigner Brenda Sutcliffe of a paper where patients with chronic OP exposure were diagnosed with frontal lobe syndrome [79]. He phoned Dr. Price's secretary with the reference. The next thing he knew his mother too was referred to see Dr .Davies for suspected OP poisoning.

It was Dr. Robert Davies who identified chronic OP induced psychiatric disorder (COPIND). Its defining criteria were proposed in a study [74] of 26 patients who had been chronically exposed (20 sheep farmers and 6 others), and again in a second study [79]. The symptoms characterised a neuro-psychiatric syndrome, any seven of which, taken together were diagnostic of COPIND. The 10 symptoms were: exacerbation of dipper's flu, personality change with affective destabilisation, impulsive suicidal thoughts, impaired concentration and memory, language disorder, reduced tolerance to alcohol, heightened sense of smell, heightened sensitivity to OPs, deterioration of handwriting, impaired exercise

tolerance related to neuromuscular disorder.

All 10 of the symptoms are described in the HSE Guidance Note MS17 (2nd ed 1987)[77], a document never circulated to the medical profession. MS17 warns "Repeated absorption of small doses, as may occur from contaminated clothing, has cumulative effects resulting in progressive inhibition of nervous tissue cholinesterase. This happens when the repeat exposures occur within the cholinesterase recovery period. Further small exposure may then precipitate the classical condition of OP poisoning. The same advice was given in a MAFF booklet 1975 'The safe use of poisonous chemicals on the farm' : "The repeated use of pesticides even in small quantities, can have cumulative effects which may not be noticed until a dangerous amount has been absorbed. This applies particularly to chemicals in the organophosphate group."

Dr. Davies saw John and his mother in June. He diagnosed them as suffering from chronic OP poisoning. They fulfilled all 10 of the clinical criteria. He recommended John should see the neurologist Dr.Goran Jamal and be given a bone scan, and prescribed paroxetine for him on the grounds it might be helpful. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) similar to prozack, which John has no intention of taking, since as he says, he is not depressed.

July 22nd John and a Gulf War veteran were invited to a meeting of 15 specialists in Exeter to assist them with the symptoms of chronic OP poisoning.

At last he had the diagnosis. Hundreds of others are not so fortunate. He has neighbours misdiagnosed for years and suffering OP symptoms and does his best to help them. He has victims ringing him up: Actellic users, sheep dippers, crop farmers, local authority workers - all with the same symptoms as himself and facing the same brick wall of denial when they attempt to get a diagnosis. Most are on prozack. There are broken relationships, broken lives and suicides. Two of his neighbours, sheep farmers, committed suicide. He believes “I have a duty to hundreds of thousands of farmers. We all have a duty to help each other.” Just as people like Shirley Bray, Richard Bruce, Joanna Wheatley had kept him going when he felt isolated, and the Countess of Mar who had phoned him up and given him back his confidence.

The advisory bodies and review committees who sit in judgement on OP victims demand evidence that their symptoms correlate with their exposure. According to MS17 the exposures can be cumulative making a correlation extremely difficult, and in any case the victim 'will be feeling so knackered he is not in a position to do anything.' When John fought off his sickness to get evidence of lowered cholinesterase activities and urine metabolites, every impediment was put in his way. Certain officials of the HSE have been and still are particularly obstructive. July 1999 he requested a cholinesterase test to find out his current levels. In the absence of baseline data his present levels might provide a useful comparison with those of July 21 98 and give correlative proof of OP poisoning. The test was refused by a Senior HSE Medical Officer on the grounds (a) 'it would serve no useful purpose'...(b) 'I am very reluctant to carry out invasive procedures unless they are of benefit to the patient concerned (sic)' and finally (c) 'Our role at HSE is not long term. We can only undertake tests at the time of the exposure.' Unfortunately this is the crux of the problem. In their evidence to the House of Commons Agriculture Committee Inquiry 1987 chaired by Sir Richard Body, into 'The effects of pesticides on human health' [80; 81p119], the. HSE admitted that it only collects data on acute cases: 'the known statistics on poisoning, ill-health and disease in agriculture do not allow us to form any judgement on illness resulting from chronic exposure.'

The British Medical Association's 'BMA Guide to Pesticides, Chemicals and Health' 1990 noted that the Agriculture Committee had identified the weakness in the legal framework: 'None of the Government agencies involved with pesticides seems to have made *any* attempt to gather data on the chronic effects of pesticides on human health.....MAFF similarly indicated they have no system for routinely monitoring any possible chronic effects caused by pesticide use or of determining the extent to which they occur.' The Guide commented: 'The Advisory Committee on Pesticides is charged with responding to data rather than acting as the initiator of enquiries' [81 p119]. However by 1992 extensive data on long term low level exposure poisoning had been collated by Enfys Chapman of the Pesticide Exposure Group of Sufferers (PEGS) and Liz Sigmund of the SW Environment Protection Agency (now the OP Information Network). This was ignored. The main result of the perceptive Agriculture Committee's Inquiry was the Control of Substances Hazardous to Health Regulations (COSHH) 1988,

and the COSHH Approved Code of Practice for the Control of Exposure to Pesticides at Work. which shifted the responsibility on to employers to safeguard their workers and on to workers and the self-employed to safeguard themselves with the approved protective clothing and careful practice. There were no plans for monitoring the effects of long term low level exposure.

12. Minute exposures : the evidence for sensitisation

It would be difficult to deduce sensitisation from John Coyte's diary when he was in continual contact with pirimiphos methyl. But after his first collapse he avoided contact and every subsequent attack bar one can be ascribed to a specific re-exposure.
(i) July 19 98 10am Treated grain with actellic. July 20 7.40am 1st collapse. Tachycardia. Breathing difficulty. Revived with oxygen. Start of 'absence episodes' and memory deficit.
(ii) July 27 Sprayed docks with mecoprop. Wearing respiratory mask. Breathing difficulty. Shaking. Could barely get back to the farm. Freezing cold. Pulse up from 48 to 80. Did not recover until July 31. Is not sure if the near-collapse was due to the mecoprop or to the Actellic-treated residue on the mask he was wearing.
(iii) Aug 8 98 7.00am Possibly had minute exposure in machinery shed. 1.40pm 2nd collapse. Tachycardia. Breathing difficulty. Revived with oxygen
(iv) Aug 24 98 OK early morning. Fetched machinery parts morning. Afternoon 3rd collapse. Tachycardia. Breathing difficulty. Revived with oxygen. There are no clues as to what exposure caused this collapse.
(v) Oct.31 98 Door of grain-shed opened by gale. He did not go inside, all he did was roll up the door. One hour later, on a visit to a neighbouring farm to see their bull, his neighbours witnessed his breathing difficulty, hands and feet shaking.
(vi) May 1999 Visited flower tent at Devon and Comwall show. m for three days. He believes the plants would have been sprayed. The perfume of the flowers might have have been sufficient or contributory.
(vii) May 26 99 Went briefly into store. Gasping for breath. Got the shakes.
(viii) June 27 99 The grain store was being made ready for the harvest and his assistant was taking out the ducting to be cleaned. John was insulated in the tractor cab and went only as far as the door of the shed where the ducting, caked with blackened dust was loaded up for him to take to the tap to be washed. His assistant washed the ducting and later, since it was now clean, John loaded it up and took it back to the shed. There were no shakes, but he did not feel well and could not think straight.
(ix) Aug 3 99 Mended a tyre in the machinery shed. He was on his knees and had shoes on. The grain store and machinery shed had all been swept out in June and the sweepings disposed of, but inevitably some dust got into the machinery area and it was not as safe as he thought. 'Nausea all afternoon. Tried to drive tractor and had to give up. Pain in both feet, heels and under arch. Lachrymation. Muzzy head. Very tired. Left eyebrow is jumping. Haven't felt so rough for along time. Aug 7 'Recovering, but still a headache and severe pain in right foot,

Toxicologists deny there is evidence of sensitisation. These episodes are clear proof of sensitisation to organphosphates. The author of MS17 [77] would call these 'cumulative exposures. This interpretation takes no account of the fact that a miniscule exposure months or years later will precipitate the classical condition of OP poisoning. and long after cholinesterase levels should have made recovery. Or that with sensitisation to OPs comes sensitisation to other chemicals. It states 'clinical effects do not generally appear until plasma cholinesterase activity has fallen to 30% of normal pre-exposure values.' This is only true for acute exposure.

Sensitisation is indicated when cholinesterase activities are no longer an objective test. AchE activities may remain in the normal range despite abnormalities in ACh transmission. an observation supported by experiences in US. (i) Environmental Health Centre. Dallas. reported that over 100 patients made ill by OP exposure often had no measurable evidence of cholinesterase deficiency, but of these many had severe chemical sensitivity [70 rev]. (ii) In an episode at a Texas manufacturing plant, workers exposed to leptophos, showed normal cholinesterase activity but all the symptoms of acute OP poisoning (memory impairment, disorientation, anxiety, drowsiness, hallucinations, tremor, headache, dizziness etc)

[82]. I suggest the workers had been sensitised by minute exposures and were responding to a larger one.

Sensitisation is a new phenomenon induced by overloading the environment. with chemical pollutants. The sensitised are in a similar situation in their inability to deal with toxic chemicals as those with immuno-deficiency who cannot meet the smallest bacterial challenge. MCS is the chemical equivalent of AIDS.

13. Disordered cholinergic transmission: the clinical evidence for chronic OP poisoning

John Coyte's diary of his reactions is a clinical blueprint, showing doctors what to look for in chronic OP poisoning and how to test for it. It is not as often described, a baffling collection of seemingly unrelated, non-specific symptoms. The symptoms are common to all OP sufferers as was demonstrated by the responses of 175 victims of OP poisoning to a postal questionnaire [79], and by the testimony of numerous others. They reflect the progressive disordering of cholinergic transmission.

1. Disordered autonomic transmission

The first effects of acetyl cholinesterase inhibition consciously experienced by the victim are an enhancement of ACh activity in the autonomic system, primarily the parasympathetic system which is innervated by the vagus and other visceral nerves via muscarinic receptors. Accumulated ACh acting as a muscarinic agonist at M_3 receptors stimulates bronchial smooth muscle contraction and secretion of bronchial mucous. Hence an early symptom was difficult breathing, a tight chest and 'awful cough'. It stimulates secretion of tears and sweat (in the latter case acting on the sympathetic system). Lachrymation is one of the first signs of OP poisoning and John was bothered for years by streaming eyes and profuse sweat. It stimulates intestinal motility and sphincter relaxation producing diarrhoea and enuresis. Desensitisation of bladder muscle receptors or over-activity of adrenergic β receptors due to anxiety may have caused bladder relaxation and water retention. It stimulates muscarinic receptors in the nucleus of the solitary tract and vomiting centre inducing nausea. His lack of balance and nausea on the kiddies' roundabout suggests in addition overstimulation of receptors in the vestibular nuclei. Vagal fibres stimulate M_2 receptors and slow the heart. Their overstimulation was reflected in bradycardia - a slow pulse, 'normal' for him at about 48 to 53 beats/min. Afferent fibres of the vagus are concerned with taste. A bitter taste was frequently reported. By 1995 his near sight was deteriorating rapidly .Activation of muscarinic receptors contract the ciliary muscle for near vision. Without his glasses all is a blur, suggesting flaccid paralysis or myasthenia (See below) and thus failure to accommodate the eye for near vision.

ACH acting on M_3 receptors dilates extracerebral blood vessels, causing OP headaches. It is clear that Actellic Dust is inhaled from treated grain as well as taken up by the skin. I suggest that to the muscarinic effects must be added those of histamine released into the bloodstream from mast cells in the nasal epithelium. Its inflammatory effect would irritate the streaming eyes and cause the initial muzzy flu- like headache. Acting on H_I receptors in bronchial smooth muscle, the nucleus of the solitary tract, vestibular nuclei and extracerebral blood vessels would exacerbate the breathing difficulty, nausea, lack of balance and 'horrendous' OP headaches.

Each time he collapsed he required oxygen; Overstimulation of bronchial smooth muscle receptors can cause paralysis producing cyanosis. Each time he collapsed his blood pressure soared and his pulse raced at over 100. Nicotinic receptors activate the autonomic ganglia where cholinergic activity governs both sympathetic and parasympathetic systems. They also activate the adrenal medulla. In general nicotinic receptors require higher levels of ACh than muscarinic for their activation, hence we can deduce that following the exposures that caused his collapses, acetylcholine accumulation was now sufficient to overstimulate the autonomic ganglia and adrenal medulla. Sympathetic overstimulation of arterial smooth muscle by noradrenaline at a α_1 receptors produced an excessive vasoconstriction and rise in blood pressure. The hospital were convinced he had a heart problem. Had they accepted that he suffered from acetyl cholinesterase inhibition this pathway could have been worked out from the clinical symptoms, substantiating the fact that he had been OP poisoned by a minute exposure.

2. Disordered motor conduction

Muscle spasms in his arms, legs and resiI' of his body were an early symptom. He records with amazement 'Suddenly my arm shot up from the elbow as I sat in the dentist's chair.' Spasms are due to an increase in the tone of a muscle or group of muscles. Rigidity as opposed to cramp implies over-stimulation of a motor neuron. Perhaps there is a clue in the fact that drugs such as mephenesin and baclofen reduce muscle tone acting mainly on the spinal cord by inhibiting first order motor neurons. The mechanism of mephenesin is unkown and baclofen has a GABA-like effect (83 pp703-4]. The involvement of nicotinic receptors in clonic spasms are indicated in a homoeopathic proving of nicotine extract, reporting 'peculiar clonic spasms that gradually increased for forty minutes' (84 vol 7 pp1-2]. In a 'proving' small doses of a substance are taken repeatedly at intervals. Its toxic properties are unfolded gradually and recorded by the prover. Nicotinic receptors acting on ion channels occur on axons and nerve terminals. In the ventral horn of the spinal cord there are cholinesterase acetyl transferase (ChAT)-containing fibres that form synaptic junctions with the cell bodies and dendrites of motor neurons (85].
Acetyl cholinesterase inhibition may have selectively affected one or more of these.
Fasciculations and increased tension are due to increased firing, followed by loss of transmission at the neuromuscular junction. Accumulation of ACh at the postsynaptic nicotinic receptors of the neuromuscular junction induce phase 1 depolarisation block. Phase 1 block occurs when excitatory nicotinic receptors are persistently activated. Sodium channels remain inactivated and the membrane cannot be repolarised for renewed activation. There is a loss of transmission and increased tension as when his 'right hand locked for several minutes.' For some days after his first collapse he had difficulty swallowing 'as if there was a huge lump stuck halfway in my throat' and he could not raise his voice, indicating excessive phase 1 autonomic motor tension in the constrictor muscles of the pharynx and intrinsic muscles of the larynx [83 p165]. Respiratory muscles can also be affected.
Phase 1 block may be followed by phase 2 where the cell partially repolarises but transmission remains blocked because the body responds to the ACh accumulation by a desensitisation or more seriously down-regulation of its receptors, matched by a presynaptic inhibition of its release. This produces myasthenia. or in extreme cases flaccid paralysis. After the exposure July 19 causing his first collapse, he suffered from a muscular weakness which must be distinguished from his longstanding fatigue. He records: "I was too weak to open a can of beans' 'It was difficult to hold a claw hammer.' His handwriting was a scrawl because he "could barely hold a pen.' This is myasthenia. [83 p149; 86p1451]. Fortunately he made a slow recovery. But he can still only move his right foot from the ankle. The loss of use of the front part from 1996 indicates a flaccid paralysis resistant to recovery. Similarly John Williams' inability to flex his left foot or to breathe using his intercostal muscles (sect.10) indicates a loss of transmission sufficient to cause flaccid paralysis.

3. Disordered sensory conduction

In addition to loss of motor transmission he has no feeling in the front part of the foot. No feeling when he pokes either the top or the ball with scissors. June 22 1999 he was given electromyographic (EMG) and conduction tests at Derriford. There was no motor response - his right toes did not jump when stimulated. But the report stated that conductivity was positive. John suggested the message was not getting through. The block in sensory transmission could again be in the spinal cord. Nicotinic receptors occur at many sensory endings [83 p159] and in the dorsal horn of spinal vertebrae there are CHaT-containing terminals that form synaptic junctions with the dendrites of sensory neurons [85]. proprioceptive stimuli, conveying information from joints and muscles on movement and position and cutaneous stimuli are conveyed from the dorsal root ganglia and dorsal gray columns to the brain stem by two tracts that end in the secondary neurons of the gracile and cuneate nuclei in the medulla oblongata. From there one pathway leads via the thalamus to the cortex, another to the cerebellum. Down-regulation of receptors on specific sensory terminals in the spinal cord could be the origin of the blocked transmission.

Aug 11 98 Three days after his second collapse, "everything went numb. His right foot, leg, arm and right side went dead.' This can only mean overactivation of sensory receptors at the level of the spinal

cord followed by desensitisation and loss of transmission. What triggered it ? If we assume accumulation of ACh at sensory receptors on spinal nerves are the cause, then I suggest this had heretofor been controlled by a transmitter inhibiting its presynaptic release. In the autonomic system the inhibitory regulator is usually noradrenaline. But in the spinal cord a number of neurotransmitters are possible modulators. It could be serotonin. He may have been anxious, perplexed at the minute exposure that caused his second collapse, and worried should he collapse out in the fields on his own. If his serotonin levels were temporarily lowered due to an inhibition of its release by a surge of adrenaline acting at α_2 receptors [87] that might account for the episode of numbness.
He has had numbness and there is now occasional tingling in the left side of his head as far down as the cheek. and a "nerve that jumps on top of my head.' Tingling reflects repeated depolarisations and numbness a loss of transmission. The jumping nerve is a fasciculation due to discharge induced by ACh accumulation at the postsynaptic receptor for the neuromuscular junction of 'an epicranial muscle. There is pain up the left side of his neck. Most sensory and motor fibres cross over from right to left and vice versa as they pass through the medulla oblongata. Hence the numbness and pain here is on the left, opposite to that in the trunk and limbs.

Is there a connection between his myoclonic spasms, the loss of use and feeling in the toes and ball of his right foot and the pains in his right leg extending from heel to calf muscle, knee and backside? Consider the clues. (i) The active constituent in *Lobelia* species is lobeline, a nicotinic agonist at antonomic ganglia and sensory terminals [84 p157]. Homoeopathic provings of *Lobelia* species induced cramp, stiffness, twitching, muscular weakness, prickling and numbness, and *a severe, widespread muscular pain* [84 vol 5 pp603-622]. .(ii) Suxamethonium is a a synthetic nicotinic agonist that causes depolarisation block at the neuromuscular junction and Ioss of electrical transmission. It is used as an adjuvant in anaesthesia to induce relaxation and 'it has been noted that there appears to be a correlation between the amount of fasciculation caused by depolarising agents as a prelude to flaccid paralysis *and the severity of post operative muscle pain.'* [83 p168]. When tone in a muscle is increased for any length of time there is (a) local tissue hypoxia or ischaemia where inadequate oxygenation of tissues is due to the increase in tone and demand (b) relative inadequacy of drainage and removal of metabolic wastes. The combination leads first to fatigue, then irritation and in time inflammatory pain [88]. I suggest that the degree of ACh accumulation ie. the number of receptors activated and the intensity of discharge determines the degree of muscle inflammation and intensity of pain. Although the ACh accumulation may subside, tissue damage is not repaired.
Tremors are an early symptom of many of the chronically OP poisoned. He frequently experienced trembling in the years that he was constantly OP exposed; and when he was attempting to avoid all contact with Actellic-treated grain he again got 'the shakes' after each of the miniscule exposures listed (except the last one when he only handled the washed ducting). Tremors and trembling are recorded by homoeopathic provers of *Agaricus,* containing the muscarinic receptor agonist muscarine [84 vol 1 pp69-125]; of *Belladonna* containng the m-R antagonist atropine[84 vol 2 pp67-128] - both *Agaricus* and *Belladonna* however have nicotinic effects; of *Lobelia* containing the nicotinic-R agonist lobeline and of the n-R agonist nicotine. Since from the provings, agonists and antagonists have the same over-stimulatory action, this suggests that OP poisoning produces tremors by interfering with a modulatory function of ACh eg. where it is inhibitory of glutamate release, or excitatory of GABA release. The pathway must involve the brainstem reticular formation -tremors *in extremis* can progress to convulsions - and its projections to the thalamus, hypothalamus, cortex and cerebellum. Again it could originate in the spinal cord: ChAT-positive neurons have been identified in the central canal cluster cells of the central gray matter [85]: 'some of whose inputs may be derived from primary afferents.... furthermore the results of physiological studies indicate that the neurons in this region respond with short latency to action potentials in modality specific for cutaneous afferents...Some neurons within the central gray matter project to the medullary reticular areaa of the brainstem. Evidence suggests these neurons could be involved in sensory modulation and/or relay function. Perhaps the strong cholinergic presence in the cluster cells and in the reticular formation accounts for the early onset of tremors, induced in OP poisoning by deranged sensory inputs from the spinal cord. These are monitored in the cerebellum and appear as involuntary muscle contractions.

It should be noted that ma study where rats were intermittently acutely injected with diisopropyl

fluorophosphate (DFP) inducing tolerance via adaptation, their tremors disappeared after 8 weeks [89] indicating that the postulated receptors modulating GABA or glutamate release were down-regulated. It can perhaps be deduced that in the totally different case of intermittent low level exposure inducing sensitisation, these receptors are among those that are up-regulated [63;65], for excitatory tremors reappear with each low level exposure.

4. Disorders of consciousness

A recent review [90 rev] proposed that acetylcholine is the major transmitter controlling consciousness. The cholinergic antagonist scopolamine is known to induce a state in which the patient is awake but unaware, and diseases that involve a loss of conscious awareness – Alzeimers, Dementia with Lewy bodies (DLB) and Parkinsonism have been treated with cholinergic agonists or AChE inhibitors to activate ACh transmission for improvement of memory, word recall, comprehension etc. In memory and cognition impairment there appears to be a deregulation of ACh receptors in the hippocampus. In DLB there is loss of conscious awareness and it is thought this may be associated with a reduction in the number of cholinergic projections to the thalamus. The thalamus is the principal relay station for sensory impulses that reach the cerebral cortex via brainstem afferents, 85-95% of which originate in the cholinergic pedunculopontine and dorsal tegmental nuclei. Selective attention as a component of consciousness is considered to be controlled by cholinergic projections from the nucleus basalis neurons of the basal forebrain to the thalamus, cortex and reticular formation.

Apart from his memory problems and difficulty in working things out, John Coyte recalls that his 'brain symptoms' did not appear until after his first collapse. (i) 'absence episodes' when he was concious but unaware: 'I walked round my sucklers and didn't know what I saw.' (ii) amnesia: 'There was a period in August that is a blank.' Fortunately he jotted down some of his experiences in his diary before they were obliterated by amnesia. 'I went out on my tractor and had to come back because I did not know where I was.' (iii) hallucinations: 'I could have opened my arms and flown round the room.' He compared notes with John Williams who told him 'I felt I could clutch rooftops and chimneys.' Hallucinogenic drugs such as the muscarinic receptor antagonists scopolamine (hyoscine from henbane) and atropine inhibit ACh transmission and induce slow wave EEG. Further suppression of ACh activity with stronger doses leads to clouding of consciousness [84] as also recorded in Hyoscyamus [84 vol 5 pp25-53] and Belladonna provings. The AChE inhibitors physostigmine and tacrine are reported to decrease psychosis (hallucinations, apathy, agitation and aberrant motor behaviour) [90].

John and fellow sheep farmer Colin Parsons report that in the early days they were intensely hyperactive, as if 'not a minute to spare...although you've got the fatigue your body is reacting against it.' This may reflect the overstimulation of glutamate due to cholinergic disinhibition of GABA, before (as postulated p14), down- regulation induced the onset of exhaustion and depression. John's 'stone cold feet even while sweating' may be a consequence of the postulated depressed thyroid activity (P14).

Perry-et al.[90] derive the evidence for their proposal that cholinergic transmission is the key component of consciousness from pathological and pharmacological studies of those suffering neurodegenerative disease and with limited or nil ability to recall their experiences, analyse their condition or communicate their thoughts.' It is somewhat ironical that they observe: "Beyond objective measures of cognition, memory and behaviour it will be valuable to explore subjective experiences that involve conscious awareness." A pity no one suggested they consult the chronically OP poisoned to help them in their researches. Members of the medical profession who class OP victims as psychiatric cases are guilty of spurning clinical data otherwise unobtainable, and may be depriving those suffering from neurodegenerative diseases of crucial information that might help treat or prevent dementia.

Analysis of John Coyte's symptoms – symptoms common to COPIND - indicates I believe, that they can all be attributed to abnormalities in ACh transmission. I suggest it may not be necessary to invoke non-cbolinergic mechanisms of OP toxicity, such as the transfer of alkyl phosphate to one or more of the myriad enzymes dependent on phosphorylation/dephosphorylation (79]. ACh does not act in isolation but in concert. Its abnormal neurotransmission has profound effects on the transmitter network and thereby on every physiological and behavioural response.

14. Objective testing

Jamal [1] lists the manifestations, markers and components of COPIND. They include: neurobehavioural and cognitive changes, psychiatric and mental manifestations, chronic fatigue, peripheral neuropathy, neuromuscular dysfunction, electro-encephalographic changes, autonomic nervous system disturbance, frontal lobe syndrome and abnormalities of cognitive evoked potentials. All are observable from clinical evidence and/or measurable by objective testing.

Objective tests of COPIND giving evidence of peripheral neuropathy include electromyography (EMG) and conduction tests, and the more sensitive measurement of jitter values [41] already described (sect 7. I). Quantitative sensory testing (QST) measures vibrotactile sensitivity [1 pp 157-159]. Autonomic dysfunction is measured via sympathetic reflex responses, or by a reduction in resting cardiac vagal tone. Bone scans assess demineralisation induced by excessive stimulation of the hypothalamic-pituitary-adrenal stress axis, with Ca^{2+} loss and over activation of parathyroid hormone. Abnonnalities in the CNS can be diagnosed by event related potentials, EEG measurements, REM sleep studies, responses to anaesthesia, cognitive tests, imaging studies from PET and SPECT scans, [1, 90] and metabolic studies using marker hormones [61].

1. Event related potentials

Event related potentials (ERPs) are cerebral waveforms generated when a person is attentive and required to distinguish one stimulus from a background of others. Thus conscious attention and its deterioration in those injured by exposure to OPs and other chemicals can be measured as 'evoked potentials.' The cognitive evoked potential (EP) or P300 is the most widely studied [43]. The subject watches or listens to a problem and the potentials evoked as they work it out are measured via non-invasive electrical recordings from the scalp. The cognitive EPs increase in latency and decrease in amplitude with increased task difficulty and also - since they depend on mental ability, in persons eg. suffering from Alzeimers. Note that there are visual and acoustic pathways to the ascending activating system (RAS) of the reticular formation, which is held to be the substrate for arousal reactions [91 p947].

Cholinergic transmission is implicated, Administration of the muscarinic antagonist scopolamine increases the latency of P300 and decreases its amplitude, effects that are reversed by the AChE inhibitor physostigmine [90]. S. Butler, Director of the Burden Neurological Institute, Bristol reported (1997) abnormal cognitive EPs in four individuals who had been acutely OP poisoned and who suffered from fatigue. They included 2 sheep farmers and an agricultural worker. He commented that the same pattern of abnormality is seen in those with CFS, but never in those whose fatigue was due to MS, post-traumatic injury *or depression* [1].

Dudley [43] chose the cognitive EP as an objective measurement of the decline in cognitive faculties self-reported by MCS sufferers to follow from exposure. 20 volunteer patients brought in the chemicals (carpet adhesives, formaldehyde, petrol, paint primer, polyurethane preservatives, perfumes etc.) which had so debilitated them they had been forced to leave their jobs. Evoked potentials were recorded in response to a visual and an auditory stimulus prior to and during a minimum half hour .exposure. Left and right visual and auditory P300 latencies were significantly prolonged during exposure with no change in the EPs of the author and his technician who served as controls. The EPs correctly identified the chemicals to which each person had said they were sensitive. There were considerable increases in symptomology: the problems with chemical odours "were of an order of magnitude the author had not seen." Two patients developed occipital seizures.

The ethics of this experiment might be questioned but the volunteers considered exposure to the chemicals in the lab was no different to what they regularly experienced, presumably in their everyday lives, since they no longer worked with the chemical that had initiated their sensitivity.

Nevertheless researchers should be clear as to what is acceptable and safe and what is not. Should tests be done on healthy volunteers as in the sarin exposure studies [41]? Or should they not rather be done on the clinically affected. via a reporting system that investigates without delay? Should they be done on mildly sensitised volunteers by briefly exposing them, as they commonly are, to dipped sheep? On no *account must those with chronic* OP *or other chemical poisoning ever be asked* to *take part.* This could be playing

with fire. Not only will it induce a return of symptoms. New ones may appear. Tremors can lead to convulsions. Breathing difficulty to respiratory collapse. Depression can be precipitated.

2. REM sleep measurements

(i) The cognitive EP can also be used to study altered states of consciousness in sleep. In healthy persons the P300 is gradually attenuated in deep sleep but reappears in those periods of rapid eye movement (REM) sleep [90] with a similar latency and amplitude to that of the waking state. REM sleep is initiated by the firing of cholinergic neurons in the pedunculpontine nuclei of the brain stem and is akin to consciousness.
(ii) Encephalograpbic (EEG) recordings of the electrical activity generated by the brain are used to monitor the state of arousal, again via electrodes placed on the scalp [83 p588] A drowsy inattentive state is associated with a low frequency EEG record, which switches to a high frequency pattern on arousal by any sensory stimulus.
(iii) Cholinergic agonists and AChE inhibitors accelerate the onset of REM sleep, shorten the latency and increase the density, whereas antagonists increase the latency and decrease the density, [63] as also does blockade of me vescicular ACh transporter vesamicol [92]. Measurements of REM sleep can be used to diagnose neurodegenerative disease: decreased REM sleep correlates with the cognitive decline seen in Alzeimers and there are reductions in its duration and density which distinguish it from depression [90]. Patients with CFS and abnormal ACh transmission and patients with myasthenia gravis where antibodies are formed against nicotinic receptors in postsynaptic membranes also have increased REM sleep latency [63].

3. Responses to anaesthetics

General (volatile) and local anaesthetics are chemical kindlers (sect.4 p10). OP sufferers report a return of symptoms following an operation or dental treatment, equal or more severe than those due to OP exposure. An SRN nurse who returned from the Gulf war totally poisoned, was ill after a dental anaesthetic and would never have another. General anaesthetics are even more to be avoided. When Mrs. Enfys Chapman broke her arm she knew from experience to avoid anaesthetics of any sort and had it set without one. A number of OP sufferers report deterioration after a general anaesthetic. One reported developing M.E. It might have been expected that these alarming accounts, presumably relayed to their GP would have alerted the medical profession, the National Poisons Unit and the licencing bodies to the OP connection insisted upon by the victims.

(i) General anaesthetics

General anaesthetics induce a loss of consciousness and with the exception of nitrous oxide, depress respiration. Evidence suggests they act by altering the activity of ligand gated ion channels, which in the cholinergic system involves nicotinic ACh receptors. The AChE inhibitor tacrine has been used since the 1960s to promote recovery of consciousness and as a respiratory stimulant. Tacrine reversal of respiratory depression suggests that volatile anaesthetics reduce bronchial muscle contractility by suppressing connections from the autonomic ganglia to the dorsal motor nucleus in the medulla oblongata. Tacrine reversal of loss of consciousness suggests volatile anaesthetic inhibition of cholinergic synapses in regions concerned with arousal: the RAS nuclei in the reticular formation and the dorsal thalamus [83 p611].

The CNS nicotinic α4β2 subtype receptor is inhibited by halothane and isoflurane, and is some 10 -35 times more sensitive than the muscle subtype [90 rev). Halothane inhibits high affinity choline uptake in rat synaptosomes and in the cat reduces ACh release from the reticular formation. At concentrations used in anaesthesia isoflurane, chlorofonn and also butanol increase channel opening rates and rates of desensitisation, indicating they are agonists and that loss of consciousness involves desensitisation. It can be envisaged that the OP poisoned have already suffered down-regulation of these receptors, ie a decrease in their number, accounting for their difficulty in concentrating (impaired

selective attention), and the anaesthetic will further set back their recovery. The fact that butanol is an α4β2 agonist suggests why the OP poisoned cannot tolerate alcohol.

Ketamine, phenycylidine, and dizocilpin are non-competitive antagonists at NMDA receptors, suppressing glutamate activity [93). If a down-regulation of receptors in the hippocampus produces fatigue and depression (sect 7 p14), then an anaesthetic of this type will exacerbate the effects of receptor loss. Volatile anaesthetics and alcohol also potentiate the inhibitory activity of $GABA_A$, glycine and $5HT_3$ receptors [94;95). It must be deduced that abnormal ACh transmission accentuates this, perhaps accounting for the observation that the OP poisoned often take hours to come round.

(ii) Local anaesthetics

Local anaesthetics (LAs) unlike general anaesthetics all have a common structure: an aromatic group linked by an ester or amide to a tertiary basic side chain. They thus include atropine and hyoscine. Belladonna and Hyoscyamus have been used as anaesthetics for over a century, a function unrelated to their anti-muscarinic activity.

LAs block Na-channels. The blocking mechanism depends on 'use dependence.' Ion channels exist in three states: resting, open in response to activation and inactivated as they close to repolarise the membrane. In most cases the LA binds more strongly to the inactivated form of the channel than to the activated or resting form. The rate of inactivation depends on the state of activation [32 p445]. Since inactivation is a slower process than activation, the more frequently the channels are opened, the greater the degree of inactivation and the more the block builds. Conversely the less frequently the channels are opened the less the inactivation - the drug is insufficiently bound and the the block fails to build [32 p405,408; 83 p332, 754]. The anaesthetic effect wears off as the drug leaks out of the closed channel.

LAs can be a clinical hazard in cases where they paradoxically *stimulate,* producing confusion, agitation, restlessness and tremor, the very symptoms experienced by John Coyte after each minimal exposure to Actellic or other chemical. The tremor can progress to convulsions, implicating RAS, but the main threat comes from respiratory depression, the symptom that caused his collapse July 20, Aug 8, Aug 24.

What are the mechanisms that produce this striking similarity? Do local anaesthetics stimulate hyperexcitability by the same mechanism as low level OP exposure?

In the case of LA overstimulation: (a) note that block is affected by gating since any agent that can increase or decrease the probability of channel opening will affect the rate of inactivation. Hence where LAs overstimulate there is some condition in the patient that modifies gating so that too few Na-channels open for the block to build. (b) LAs have a secondary function in that they themselves modify gating via an influence on the membrane potential [83 p746]. It can be deduced from the excitatory symptoms that the LA must modify the gating so that the membrane is depolarised at more positive potentials, an effect unnoticed when it acts as a blocking agent.

In the case of the chronically OP poisoned given a local anaesthetic: LAs block voltage gated Na-channels and the chronic OP patient is anaesthetised as expected. But LAs also block ligand gated nicotinic-ACh receptor channels. Down-regulation of the nACh receptors would have reduced the number of channels opened by cholinergic stimulation so that in those channels the block fails to build. But the LA has modified the gating, shifting the depolarisation to more excitatory positive potentials. The overexcitation may be masked since the important voltage gated channels are blocked, but it will be countered by yet further suppression of ACh release at affected nACh channels. The OP victim's symptoms are exacerbated, or if he was recovering they return.

Why do those who deny the existence of COPIND not use event related potentials and REM sleep studies to test the validity of their assertions that the chronically OP poisoned "suffer from a psychiatric illness that they prefer to interpret as environmental sensitivities" [3]? The response of the chronically poisoned to volatile and local anaesthetics is independent of mental state. Why has there been no concern to investigate it? A bad reaction to anaesthetics is one more instance of evidence thrown away. It is clearly an inadvertent form of objective testing.

5. The persistence of pirimiphos methyl: undisclosed fonnulations ?

Richard Bruce has raised repeatedly with the manufacturers and the PSD that the half lives given for pirimiphos methyl are false (3 -25 days in soil, 4.2 days in water in which it hydrolyses, and less than 1 day if exposed to sunlight [76 pp3340]. Richard had been sensitised and suffered OP symptoms from years of treating grain with Actellic WD40, a variation of actellic D, the spray formulation of pirimiphos methyl. But he was irreversibly poisoned when 30 gallons of diluted WD4O had been left in the sprayer for 6 months and he was required to clear out a drain down which the diluted Actellic had been discharged. Zeneca assured him that hydrolysis would have rendered it innocuous in a few days. A six month old solution could not have been the cause of his illness. To test this assertion, 1997 he diluted some of the Actellic with water and left samples on his window sill. One year later and again two years later the same solution killed flies in 3 to 4 minutes. Neither the manufacturers nor the Advisory Committee for Pesticides (ACP) in their Evaluation Document [76] heeded his reports of the experiment.

The half-lives would appear to be in conflict with the Evaluation Document's statement p80 that residues in treated grain 'declined slowly or not at all with time' and persist in the flour (see below), but Zeneca explain that Actellic only remains active on dry, inert surfaces such as wood, metal and also grain with less than 15% moisture, ie. where it does not hydrolyse. Richard's experiment demonstrates that the toxicity persists in water and in sunlight. The matter could be settled if the experiment was repeated. Should Richard be proved right then either (i) the half lives for pirimiphos methyl are incorrect. This is unlikely. A glance at the chemical structure confirms that it is indeed very easily hydrolysed. Or (ii) The persistent toxicity of Actellic D and also Actellic 2% dust (see below) is due to the presence of some 'enhancing agent' whose identity is not disclosed on grounds of commercial secrecy. If the enhancing agent is another OP it is likely to be an aromatic compound because aryl groups hinder hydrolysis. Water-octanol partition coefficient values increase with aryl substitution, conferring poor water solubility and resistance to hydrolysis and enabling some OPs to persist in an aquatic environment. Examples are leptophos, dichlofenthion, chlorpyriphos [96]. If the enhancing agent is a non-OP toxic to insects, it would be toxic also to those who have been chemically sensitised.

What was the point of only evaluating pirimiphos methyl? Why did the ACP not also evaluate the formulations of Actellic?

Richard sent John an empty bag of Actellic 2% dust that a friend had washed out twice with soapy water, rinsed and left in the rain and sunlight. He parcelled it up with a mask over his face. John was overcome when he unwrapped it and he too had to wear a mask to handle it. Actellic 2% dust must contain the same or a similar persistent enhancing agent.

This raises questions. MS17 mentions contaminated clothing. as a source of cumulative exposure [77]. The above suggests that the sensitised can detect Actellic residues even *if the clothing is washed.* It suggests that the protective clothing itself could be toxic to the sensitised. It may be the explanation of John's malaise when he loaded the 'clean' ducting.

The PSD were unable to provide Richard with the full formulation details of Actellic D because "the Plant Protection Product Regulations 1995 (as amended) state that 'Ministers shall treat any information submitted...as confidential to the extent that in the opinion of the Ministers that information contains industrial or commercial secrets.' This principle of confidentiality is also enshrined in the 'Code of Practice on Access to Government Information.' (letter to Richard Bruce from Environment and Residues Policy, PSD Ist June 1999)

We require the impending Freedom of Information Act to include - what the White Paper now excludes - public disclosure by the manufacturers of their chemical formulations, whether licenced or with licence applied for and whether at the time believed toxic or safe. Patent law should cover their commercial interests.

In the meantime *I urge COT, the Advisory Committee for Pesticides and the EU Scientific Committee for Food to have the Bruce experiments with Actellic* D *and Actellic* 2% *dust repeated by an independent body, and if proven, ascertain from Zeneca the identity of the enhancing chemical(s) and compel withdrawal of Actellic formulations from the market.*

16. Pirimiphos methyl in the food chain

John Coyte and Richard Bruce worry that pirimiphos methyl is going into the food chain. Residue levels in wheat and barley are given in the Evaluation Document [76 pl24] as 5mg/kg. 80-90% is removed in the bran when milling white flour, 50% when milling wholemeal. The BMA 'Guide to Pesticides, Chemicals and Health' first published 1990 [97] noted that MAFFs Research Consultative Committee's Residues Sub-Group [98] were concerned over pesticide residues in bran and also in beer. In US pirimiphos methyl is not allowed to be used on stored grain, the for very reason that it persists in the husk. The BMA Guide also noted that a survey on infant foods by MAFFs Working Party on Pesticide Residues 1987, found that rusks were the most widely contaminated with pesticide residues: 18 out of 31 samples of rusk had pirimiphos methyl at higher levels than in other infant foods [97 rev p128].

The maximum theoretical daily intake ingested by an adult via wheat is calculated to be 127mg/d : O.02mg/kg bw/d for a 60kg adult and above the ADI 0.03mg/kg bw/d. For a child of 30 kg and an infant of 7.5kg, the theoretical daily intakes are calculated as 0.04mg/kg and 0.05mg/kg bw/d respectively [76]. These calculations are of limited value. They take no account of :

(i) The possibility that the Actellic is not properly mixed in or may contain higher amounts than that recommended, either through carelessness or deliberately because as noted by the BMA Guide 'stored produce may also be subjected to repeated pesticide treatment' [97 p124;93], due to transfer to other stores. The minute fraction of samples tested may not pick up these larger residues. Grain going into Intervention is reported to be particularly liable to over-treatment.

(ii) Synergistic effects due to the presence of other toxicities in food or to which a person might be exposed by other routes.

(iii) The intolerance of the sensitised to levels below the ADI. Those who must restrict themselves to organically grown foods to avoid adverse reactions will testify that the ADls are inadequate to protect them. The fact that an identical admissible operator exposure level (AOEL) of 0.03mg/kg bw/day has proved toxic in cases of long term low level exposure is evidence that a similar ADI by ingestion may invoke harmful reactions in the sensitised.

(iv) An additional margin of safety is required for a developing organism. No recognition of this is given in UK, although the BMA Guide [81 p 126-8] drew attention to the risk to children, quoting evidence produced in United States [98]. The EU Commission is now sufficiently concerned to rule that the ADI for any pesticide in any one product, set at 0.lmg/kg product for adults be reduced to 0.0lmg/kg in processed cereal-based foods, baby foods and foods for infants and young children (Directive 1999/39/EC, to come into effect not later than 30 June 2000.)

Animal studies as well as evidence from human poisonings show that the developing foetus, babies, infants and children up to 5 years are more sensitive to pesticides particularly OPs than adults and older children [99 rev]. Not only does 75% of brain development occur in the first two years of childhood [100], but OPs at very low levels of exposure are toxic to the developing brain [101]. The toxicity is exacerbated by the fact that the blood-brain barrier is not fully developed until about 1 year of age [102] and that infant animals often have less developed detoxification systems than older members of the species [103;104]. The US National Research Council in a study of pesticides in the diets of infants and children concluded: "The data strongly suggest that exposure to neurotoxic compounds at levels believed to be safe for adults could result in permanent loss of brain function if it occurred during the prenatal or early childhood period of brain development." [104]. The Environmental Protection Agency (EPA) reported: "OP exposure can produce long term behavioural and functional damage to the nervous system in the absence of observable signs of toxicity, and with little correlation with cholinesterase levels "[105].

Worry that American babies, infants and children were exposed to higher levels of pesticides per body weight than adults in their food and from other sources, and furthermore that none of the OPs widely found in the food. supply had been tested for neurotoxicity, led to the. incorporation of stricter controls in the US Food Quality Protection Act (FQPA) 1996. This is a landmark Act. (i) It requires the

risk from the aggregate intake of pesticides with a common toxic mechanism to be taken into account. (ii) Before a pesticide can be allowed in the food it must be safe for babies, infants and children. (iii) In their case it overturns the previous demand for proven evidence of toxicity: in the absence of complete and reliable data on the pre- and post-natal neurotoxicity of a pesticide "an additional ten-fold margin of safety for the pesticide chemical residue should be applied for infants and children." (FQPA section 408(b)(2)(C)(iii)(II)). Since the main US anxieties are of pesticide levels in fruit and vegetables, there is no question of restricting the margin of safety to 'infant formulae and follow-on formulae' as in the EU Directive.

John and other OP victims believe that respiratory problems due to OP poisoning have not been diagnosed. He learnt from the National Asthma Research and Respiratory Training Centre that the highest number of asthma cases is among bakery workers. This might be ascribed to flour dust and/or to the increasing populations of actellic-resistant mites (Farmers' Weekly 3.6.98 p62, 25.7.98 p53). But perhaps intermittent low level exposure to the 5mg/kg Actellic present in the unmilled grain is a factor? He asks why the incidence of asthma is as high in country children as in the air-polluted towns? Why are respiratory problems severe in the Highlands and Islands where sheep are a major source of income and all are double-dipping (dipping twice a year)? Why are there so many children with ME symptoms resembling those of chronic OP poisoning? Are there other cases in the elderly of misdiagnosed Alzeimers?

The usual tactic for a manufacturer to adopt when a product's toxicity is becoming public knowledge and there is threat of litigation, is to quietly withdraw the product. Another tactic is to withdraw it from a specific use.

Could this be the explanation for the appearance of a 2% Actellic Dust, labelled *'Not for admixture with cereals* and *animal feeding stuffs'* ? Boxes of Actellic 2% Dust have been arriving on farms that had ordered their usual quota for treating this year's (1999) harvest bearing a label entirely different from all previous labels, in particular it reads : *(i) Not for* admixture *with cereals and animal feedstuffs (ii) For use in grain stores and in domestic industrial and public health outlets* These included buildings for industrial and catering establishments, domestic premises, refuse tips, slaughter houses, granaries, provender mills. *(iii) For use only by professional operators (iv)* The caption *Zeneca Crop Protection* was missing *(v)* The registration number MAFF 06931 had been replaced by *HSE* 4881.

It was a sticky label and when this was peeled off the normal MAFF label appeared underneath:

"For use only as an insecticide in food storage practice" "Use - wheat, barley or oats including barley for malting, milling wheat and seed oilseed rape and linseed."

The suppliers were contacted and gave assurances it was all right to apply it to the grain. When questioned, the PSD and Zeneca denied all knowledge of the new label. Perhaps those particular boxes were sent out inadvertently, giving mis-timed notice that Actellic is to be switched to other uses.

May 23rd 1999 I attended a MAFF meeting at Tolworth to discuss another matter. I happened to mention that pirirniphos methyl was incorporated into stored grain and was going into the food chain. A senior MAFF toxicologist expressed horror and was adamant this was not the case. *Feed* grain was not treated with organophosphate. Only *seed* grain was treated with it. At the time I was at a loss he could be so misinformed. Now I ask the question: was MAFF already preparing for the revocation of Actellic for the specific use 'treatment of stored grain' ? If true we have to thank Richard Bruce, John Coyte and all those victims of Actellic poisoning who fought for its effects to be publicly known. They fought not just for themselves but for all of us, and particularly the under five year olds whose risks from neurotoxicity have been totally disregarded.

But are the victims to be left in limbo? 1998 the Official Group on OPs reported [106 p80] that in 1996 a BMA Working Group had suggested to the Chief Medical Officer the setting up 'of a clinical database of case histories, clinical details and other evidence provided by clinicians, scientists, patient organisations and others with a *bona fide* interest. They suggested that this information might be useful to GPs, those experiencing symptoms, researchers and the - interested public such as farmers.
...Such case histories could be used for study and might help to bring about an understanding of possible

individual susceptibility or whether there are operational circumstances which could increase risk.' .....The Official Group considered the idea should be pursued and proposed that the data collected by Enfys Chapman of PEGS and Liz Sigmund of the OP Information Network could be the basis for further work. Apart from the 'Scope' survey to identify those among the chronically poisoned who might have low paraoxonase activities and inadequate detoxification [107], what has been done?

A review by Dr. D.E.Ray for the Institute for Environment and Health (IEH) 1998 of putative chronic neurotoxic effects in humans resulting from OPs, concluded that prolonged low level exposures 'are not likely to be responsible for any subjectively adverse health effects' [108]. The review rejected a large number of clinical and epidemiological studies on grounds of unreliable study design. The Official Group - for whom the main issue was the postulated long term effects following long term exposure - clearly felt that the COT Working Group should examine questions not answered satisfactorily by the IEH review.

The relevance of 'study design' must be challenged. The totality of clinical symptoms in hundreds, perhaps thousands of victims is sufficient to establish chronic OP poisoning [79]. The manufacturers, licencing bodies, HSE and National Poisons Unit having dispensed with post-surveillance monitoring, should now be paying heed to those who are doing it for them.

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