Patient number	Age (years)	Sex	Source of request	Clinical details on request form	Tests requested	Final diagnosis
1	76	M	GP	Lethargy	TFT, UE, LFT	Viral encephalitis?
2	64	M	GP	TATT, joint pain	TFT, UE	Hypopituitarism, normal MRI
3	29	M	GP	Hot flushes	TFT, glucose	Pituitary adenoma
4	78	F	GP	TATT, joint pain	TFT, UE, LFT, calcium	Pituitary adenoma
5	80	F	Ward	Leg oedema, HF	TFT, UE, LFT	Empty sella syndrome
6	86	F	Ward	Anaemia	TFT, UE, LFT, calcium	Hypopituitarism, normal MRI
7	73	F	GP	TATT, weight loss	TFT	Hypopituitarism, cause?
8	55	M	GP	Exophthalmic	TFT	Pituitary adenoma
9	75	F	GP	TATT	TFT, LFT	Prolactinoma
10	77	M	Ward	Off legs	TFT, UE, LFT, calcium, CRP	Pituitary adenoma
11	69	M	GP	Pallor, weak	TFT, UE, iron, ferritin	Pituitary adenoma
12	62	F	GP	Lethargic	TFT, UE, LFT, lipids	Hypopituitarism, normal MRI
13	54	F	GP	Diabetes, hypothyroid?	TFT	Empty sella syndrome
14	54	M	OPD	Weight gain, deep voice	TFT	Hypopituitarism, normal MRI
15	69	F	GP	Pale	TFT, UE, glucose	Died, no post mortem
16	84	M	Ward	Postoperative, unrousable	TFT, UE, LFT, calcium, CRP, BGas	Non-thyroidal illness
17	38	F	Ward	Porphyria	TFT, UE, LFT, calcium, CRP	Non-thyroidal illness

GP=general practice, OPD=outpatient department, TATT=tired all the time, HF=heart failure, TFT=thyroid-function tests, UE=urea and electrolytes, LFT=liver-function tests, CRP=C-reactive protein, BGas=blood gases, MRI=magnetic resonance imaging.

Table 2: **Demographics and tests requested for previously undiagnosed patients with hypopituitarism**

grounds, and hypopituitarism was confirmed in each patient. This group of patients (median age 50 years, range 22–74, four women) was significantly younger than our study patients, who had hypopituitarism identified by thyroid-function tests (p=0·035, Mann Whitney *U* test). Three of the 11 patients referred to hospital had panhypopituitarism and seven had low or undetectable cortisol concentrations. Over the same period, the ratio of primary to secondary hypothyroidism detected by our test strategy was 20/1.

Reported incidence of hypopituitarism is eight to nine new adult cases per million population per year.[5] Our findings in the Liverpool population of 471 000 served by our hospital, suggest an incidence of 55 cases per million population per year (95% CI 36–81), of which 32 per million per year (18–53) might be undiagnosed if a first-line thyrotropin strategy is adopted.

We suggest that hypopituitarism is an under-diagnosed disorder with non-specific symptoms, especially in elderly patients, and is more common than previously reported. Hypopituitarism is a treatable disorder that can have serious clinical consequences if panhypopituitarism develops. Cortisol concentration was undetectable in 40% of our patients, and one patient died before any action was taken on our results. When interpreting the results of thyroid-function tests, hypopituitarism should be considered as a possible diagnosis when thyrotropin concentration is in the reference range but when concentrations of total thyroxine, free thyroxine, or both are low. We strongly advocate measurement of serum thyrotropin concentrations together with either total or free thyroxine concentrations as first-line thyroid-function tests.

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Chronic nervous-system effects of long-term occupational exposure to DDT

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Dichlorodiphenyltrichloroethane (DDT) is a compound with moderate toxicity that is judged to be safe for occupational use, although little is known about its long-term effects on the human nervous system. We investigated chronic nervous-system effects of long-term occupational exposure to DDT by comparing the neurobehavioural performance of retired malaria-control workers with a reference group of retired guards and drivers. DDT-exposed workers did worse on tests assessing various neurobehavioural functions than controls; performance significantly deteriorated with increasing years of DDT application. Our results could not be explained by exposure to cholinesterase-inhibiting pesticides or other potential confounding factors.

Dichlorodiphenyltrichloroethane (DDT) has been widely used for pest control, but is now banned in many countries because of its persistence in the environment and associated harmful effects. Discussions are continuing about use of DDT in the control of malaria,[1,2] despite little knowledge of its chronic effects on the human nervous system.[3]

By checking every second file of the personnel register of the Ministry of Health of Costa Rica from 1950 to 1997, we identified 59 retired men aged 55–70 years who had been involved in DDT use between 1955 and 1996. The men had all been exposed to DDT for at least 2 years. We identified, as controls, 64 male retired guards and drivers with the same ages and educational backgrounds, from the 1990–92 and 1995–97 Costa Rica Social Security staff lists. Controls had all been employed for at least 2 years between 1955 and 1996. We approached all candidates by home visits and asked them to participate in a study of current health status, with emphasis on neurobehavioural functioning in relation to their work history.

We located 41 (69%) of the 59 exposed men, and 47 (73%) of the 64 controls. Of these, 36 (88%) and 31 (66%), respectively, participated in our study. Nine of the exposed group were excluded from analysis because of epilepsy(1), cerebral haemorrhage(1), cholinesterase-inhibiting pesticide intoxication(3), or recent insecticide

Test	Mean test scores (SD)*		Adjusted differences† (95% CI)
	Exposed (n=27)	Referents (n=27)	
Cognitive			
Attention			
Verbal, digit span (forward and backward)	5·6 (1·9)	7·0 (2·6)	−1·4 (−2·7 to 0·0)‡
Visual, digit vigilance (s)	262 (71)	250 (53)	25·5 (−12·9 to 63·9)§
Visuomotor			
Speed, digit symbol	18·7 (6·9)	21·7 (7·2)	−4·4 (−8·5 to −0·2)‖
Sequencing, trails-A (s)	72·3 (26·5)	65·3 (21·8)	20% (0 to 43)¶
Steadiness, pursuit aiming II	67·7 (34·7)	75·8 (28·7)	−8·4 (−26·8 to 10·0)§
Motor			
Simple reaction time (ms)	376 (115)	319 (72)	34·6 (−18·8 to 88·1)
Finger tapping speed, both hands	77·8 (18·7)	89·0 (13·9)	−9·0 (−18·6 to 0·7)
Dexterity, Santa Ana dexterity, both hands	49·4 (13·8)	53·5 (8·5)	−5·0 (−11·1 to 1·1)
Dexterity, Purdue pegboard, both hands	21·4 (3·0)	23·0 (3·2)	−1·9 (−3·7 to −0·1)**
Grip strength, dominant hand (kg)	28·7 (6·8)	33·1 (6·2)	−2·6 (−6·3 to 1·1)
Pinch strength, dominant hand (kg)	4·0 (1·0)	4·6 (1·1)	−0·5 (−1·1 to 0·1)
Sensory			
Vibrotactile sensitivity (Vibratron II)			
Thumb, dominant hand (Hz)	2·3 (1·6)	1·9 (0·7)	18% (−5 to 45)¶
Big toe, dominant foot (Hz)	6·5 (3·5)	6·3 (3·7)	2% (−34 to 58)¶
Near visual contrast sensitivity, mean of both eyes (cycles per degree)			
1·5	41·8 (10·4)	46·0 (7·7)	−1·8 (−6·4 to 2·9)§
3·0	62·1 (14·9)	69·5 (19·7)	−3·7 (−11·9 to 4·5)§
6·0	54·6 (22·3)	64·1 (21·0)	−2·5 (−10·4 to 5·5)§
12·0	28·9 (23·3)	64·1 (21·0)	−2·7 (−9·0 to 3·5)§

*Number correct responses unless other units specified. †Adjusted for age, loss of consciousness, and years exposed to cholinesterase-inhibiting pesticides in malaria control. ‡p=0·048. §Adjusted for visual acuity (near visual contrast sensitivity 18 cycles per degree). ‖p=0·043. ¶ Relative differences (%) presented because log-transformed test outcomes used a multiple regression analysis.**p=0·049.

Table 1: **Test scores of DDT-exposed individuals and controls**

exposure(1). Three were excluded as they had never applied DDT.

Four controls were excluded because of Parkinson's disease(1), childhood spastic paralysis(1), occupational DDT exposure, (1) or cholinesterase-inhibiting pesticide intoxication(1).

We compared neurobehavioural test performances of 27 former malaria workers (mean age 64·3 years [SD 3·7], mean education years 5·1 [2·0]) with that of 27 controls (64·9 [2·7], 6·0 [2·1]) of similar socioeconomic status (individuals were assigned low, medium, or high socioeconomic status on the basis of a checklist completed after visiting the participants' homes). The individuals underwent clinical examinations, responded to questionnaires on occupational history, health, and lifestyle, and neuropsychological and psychiatric symptoms, and completed 17 neurobehavioural tests assessing cognitive, motor, and sensory functions. Current general health status, current medication, and medical history did not differ between exposed individuals and controls. The two groups had similar blood pressure, resting pulse rates, cataract formation, blood sugar, cholesterol, γ-glutamyl transpeptidase, bilirubin, and serum and red blood cell cholinesterase concentrations. Standard neurological assessments by a clinician showed no abnormalities.

Based on questionnaire results, and staff registers and technical reports from the Ministry of Health, the number of years of DDT application (mean 4·6 years [SD 4·6]; 1955–86) and exposure to cholinesterase-inhibiting pesticides (3·6 [5·9]; 1971–96) were estimated. Based on the 75th percentile of DDT-application years, medium (n=19) and high (n=8) exposure groups were defined (cut-off point 6 years). 18 of the 27 exposed were members of an organisation for retired vector-control workers and were aware of the possible health risks from DDT. We told these individuals that deliberate poor test performance would be identified and result in exclusion from the study. Affiliated workers had more DDT-application years (mean 5·2 years [SD 5·2] *vs* 3·5 [2·6]) than non-affiliated workers, and were slightly older (64·6 [3·5] *vs* 63·9 [4·3] years).

We did multiple linear regression analyses for all neurobehavioural tests, for exposure (yes or no), exposure type (none [control], medium, or high), and years of DDT application (assigning 0 years of DDT application to controls) as explanatory variables. Test outcomes that did not follow a normal distribution were log-transformed to obtain a normal distribution. Additionally, outcomes of the symptom questionnaires were dichotomised at more than six symptoms (Q16) according to Hogstedt and colleagues,[4] and at the 50th percentile of the study population (brief symptom inventory, grand total >28). We calculated odds ratios by multiple logistic regression. We also studied the effect of confounding variables on test outcomes for linear and logistic modelling. Variables that changed the model meaningfully (entering the model with a p value <0·10 and changing the β of DDT exposure by at least 5%) were kept. Results were adjusted for effects of age, loss of consciousness, years exposed to cholinesterase-inhibiting pesticides in malaria control, and, if necessary, visual acuity (nearby visual contrast sensitivity at 18·0 cycles per degree). Adjustment for years of education, smoking habits, lifetime alcohol consumption, history of malaria, caffeine use, solvent exposure, membership of an organisation for retired vector-control workers, body-mass index, blood sugar concentration, reported diabetes, and other possible confounding variables did not change results.

Table 1 shows test outcomes for controls and DDT-exposed individuals, and the adjusted differences in performance between them. The exposed group had overall poorer performance, with mean decrease in performance of up to 20%. Verbal attention and visuo-motor speed and sequencing differed most between groups. The deficits were more apparent in the high-exposure subgroup for all tests except for finger tapping (data not shown). The exposed group also reported significantly more neuropsychological and psychiatric symptoms than did controls (odds ratio for Q16 3·98 [95% CI 1·02–15·63] and for brief symptom inventory 7·25 [1·87–27·78]). The results for years of DDT application as the explanatory variable yielded significant exposure-effect relations for five tests in cognitive, motor, and sensory domains, as well as for the symptom questionnaires (table 2).

Our results could not be explained by exposure to cholinesterase-inhibiting pesticides. For four of the tests in table 2 (ocular motor sequencing, motor reaction, speed, and strength), the number of years of exposure to cholinesterase inhibitors was also related to test outcome. However, this effect was additional to that of DDT and was significant for only two tests: motor reaction (p=0·012) and grip strength (p=0·008). DDT-application years contributed substantially to the variance of the models. Member status did not confound the exposure-effect relations for any of the tests presented in table 2. Even the symptom questionnaires were unaffected by member status.

Our results suggest that chronic occupational exposure to DDT is associated with a permanent decline in neurobehavioural functioning and an increase of neuropsychological and psychiatric symptoms. The

Test	Effect per DDT-application year ß*(SD)	p	R^2	Proportion of explained variance attributable (%)		
				DDT	Chl	Age
Cognitive-visuomotor						
Sequencing, trails-A (s)	0·024 (0·011)†	0·032	0·17	45	26	26
Motor						
Reaction, simple reaction time (ms)	10·4 (3·0)	0·001	0·36	56	31	13
Grip strength, dominant hand (kg)	−0·6 (0·2)	0·010	0·29	46	48	5
Pinch strength, dominant hand (kg)	−0·08 (0·04)	0·034	0·16	65	34	0
Sensory						
Near visual contrast sensitivity, mean of both eyes 1·5 cycles per degree	−0·8 (0·2)†	0·003	0·54	26	0	0
Affect or symptoms						
Questionnaire - 16 (number of yes answers)	0·5 (0·1)	0·001	0·36	59	5	9
Brief symptom inventory (grand total)	4·4 (1·2)	0·001	0·29	83	12	0

Chl=cholinesterase inhibiting pesticides. *Adjusted for age, loss of consciousness, and years exposed to cholinesterase-inhibiting pesticides in malaria control. †Multiple regression analysis was done with log-transformed test results. Exponent of presented β results calculated in a factor of 1·025, which means a 2·5% increase in test-score per DDT-application year. This results in an increase of 1·7 s per DDT-application year for the average trails-A score (average=68 s, 68×1·025=69·7). †Adjusted for visual acuity (near visual contrast sensitivity 18 cycles per degree). Visual acuity attributed 73% to explained variance.

Table 2: **Significant relations of DDT-application years with test outcome (n=54)**

amount of decline was directly associated with years of DDT application. Even small changes in nervous-system functions induced by toxic exposure have important repercussions in elderly people because of their reduced capacity to compensate for impairment, resulting in accelerated ageing.[5]

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Brainstem activation specific to migraine headache

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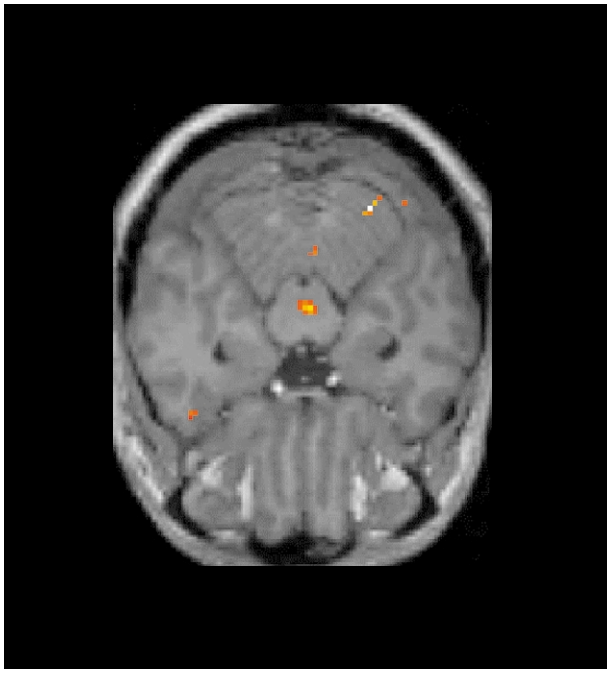
Findings from functional imaging studies have shown activation of the brainstem during migraine without aura (MWOA) and activation of the hypothalamus during cluster headache. We assessed a patient with cluster headache and migraine by positron emission tomography during an active cluster headache after he had taken 1·2 glyceryl trinitate. The patient developed a typical MWOA, during which we saw activation in the dorsal rostral brainstem. There was no activation in the region of the hypothalamus. Our findings provide evidence that migraine involves the brainstem, and show several areas involved in cluster headaches. Our data show the potential for objective distinction between primary headache syndromes with functional imaging, in disorders hitherto distinguished on clinical grounds.

Primary head-pain syndromes, such as migraine and cluster headache, are diagnosed on clinical grounds. Early studies identified the main pain-producing structures in the head, which included blood vessels, especially the proximal cerebral and dural arteries, large veins, and venous sinuses. Stimulation or distention of different vessels causes pain in different parts of the head. The throbbing quality of the pain and relief from vasconstrictive agents lent support to these studies and formed the basis of the concept of a vascular origin to migraine and cluster headache. However, migraine and cluster headache are clinically, epidemiologically, and therapeutically distinct. Findings from studies with positron emission tomography have shown activation of the brainstem in migraine without aura (MWOA),[1] and the posterior hypothalamus in cluster headache.[2] These findings suggest that specific brain regions are pivotal to the pathogenesis of clinically distinct primary head-pain syndromes.

A man aged 43 years had a history of cluster headaches since age 18 years and MWOA since age 14 years. He



Brainstem activation during acute migraine
Positron emission tomography mapped on to brain magnetic resonance image showing activation in dorsal rostral brainstem.