

Hydrogen sulfide exposure without loss of consciousness: chronic effects in four cases

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Adverse effects of acute exposure to hydrogen sulfide (H_2S) are well documented, but long-term effects of occupational exposure to low levels of the gas are not. To evaluate effects of such exposure we performed physical, neurologic, psychiatric, and chemosensory (smell and taste) examinations of four workers who were present but did not lose consciousness when the gas was accidentally released at a construction site. None of the four workers tested positive for functional problems, but all met diagnostic criteria for at least three, and up to eight, H_2S -induced neuropsychiatric clinical disorders and from zero to two subclinical disorders. All four had abnormal P300 evoked responses (electrical neurophysiologic tests of brain waves). Our data indicate that exposures to even relatively low concentrations of H_2S are hazardous. A rigorous epidemiologic investigation of persons who work with H_2S is warranted. *Toxicology and Industrial Health* 2002; **18**: 51–61.

Key words: chronic neurotoxicity; hydrogen sulfide; industrial exposure

Introduction

Hydrogen sulfide (H_2S), a colorless gas easily recognized at 0.025 ppm by its distinctive rotten-egg odor, is used in the refining and tanning industries. Over the past three centuries, many neurotoxic effects have been reported due to exposure to this gas (Ramazzini, 1713; Reiffenstein *et al.*, 1992) and since the 1980s such effects have received growing attention. Concentrations considered neurotoxic have gradually dropped from 700–1000 ppm 50–100 years ago to 0.6 ppm in 1987 (Gaitonde and Sellar, 1987). In the USA, the Occupational Safety and Health Administration (OSHA) set allowable concentrations at 10 ppm

over an eight-hour day – a considerably higher level than most European countries allow (Norback and Norback, 1988). The World Health Organization (WHO) has set community standards as low as 0.003 ppm (WHO, 1982; 1987; Glass, 1990).

Medical literature documents adverse clinical effects of the entire neuraxis. In the brain, H_2S causes an encephalopathic and neurasthenic-like syndrome, exacerbation of seizure disorders, and headache (WHO, 1982; Kangas *et al.*, 1984; Tavis *et al.*, 1984; Arnold *et al.*, 1985; Audeau *et al.*, 1985; Whitcraft III *et al.*, 1985; Hoidal *et al.*, 1986; Gaitonde and Sellar, 1987; Mack, 1987; Norback and Norback, 1988; Jaakkola *et al.*, 1990; Tvedt, Skyberg *et al.*, 1991; Kilburn, 1993; Kilburn and Warshaw, 1995b). Cranial nerves found to be affected include cranial nerve I, the olfactory nerve, with hyposmia or anosmia (Gaitonde and Sellar, 1987; Tvedt, Skyberg *et al.*, 1991), cranial nerve II,

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the optic nerve, with optic or pathway dysfunction (Tvedt, Skyberg *et al.*, 1991), and cranial nerve VIII, the vestibulocochlearis or its cochlear labyrinthine extension (Tvedt, Skyberg *et al.*, 1991; Reiffenstein *et al.*, 1992). Peripheral nervous system sequelae may include generalized polyneuropathy, with neuritis (Zyer, 1995), as well as autonomic neuropathy or instability as manifested by orthostasis, impotence, and dysregulation of bowels (Glass, 1990; Kilburn, 1993). Since symptomatology is not uniform, ancillary tests have been used to detect neurologic effects due to exposure to H₂S (Wasch *et al.*, 1989; Callender *et al.*, 1993).

Many reports indicate that on exposure to high concentrations with loss of consciousness, if death does not intervene, recovery is rapid with minimal neurologic sequelae (Burnett *et al.*, 1977; Whitcraft III *et al.*, 1985; Mack, 1987; Anonymous, 1993; Snyder *et al.*, 1995). But a number of authors note chronic sequelae after such exposure (Ramazzini, 1713; Tvedt, Edland *et al.*, 1991; Tvedt, Skyberg *et al.*, 1991; Vicas, 1992; Kilburn, 1993; Kilburn and Warsaw, 1995a,b). A few address the acute effects of H₂S exposure without loss of consciousness (Hahtela *et al.*, 1992); the long-term sequelae in such cases, however, have not been well investigated (Jaakkola *et al.*, 1991). The purpose of the present study, therefore, is to assess long-term effects in four cases of H₂S exposure without loss of consciousness in order to add to this base of knowledge.

Subjects and methods

Subjects' case vignette

On 8 January 1993, over a 2.5-hour period, approximately 900 pounds of H₂S were accidentally released into the environment at a construction site at a gas refinery in St. Crois, Virgin Islands. Workers noted chemosensory phenomena consistent with H₂S exposure, i.e., the smell of rotten eggs, and a strong metallic taste. None lost consciousness but all experienced a variety of irritating local effects, i.e., lacrimation, eye irritation, nausea, vomiting, headache, sore throat, and skin irritation. Atmospheric concentrations of H₂S were not determined at that time, but similar releases had been documented over prior months

with concentrations as high as 243 ppm recorded in the work area.

Because of their persistent complaints of neuropsychiatric symptomatology over a period of about a year, four workers who had been approximately 500 feet from the release site underwent extensive evaluations.

Clinical evaluation

The author examined the four subjects and recorded their complete histories about one year after their accidental exposure.

Each subject estimated the duration of his exposure to H₂S and other potential neurotoxin sources at work, home, or other sites and hobby situations, then underwent three to four hours of history taking [neurologic, psychiatric, chemosensory (smell and taste), and neurologic family history] and medical, neurologic, and psychiatric examinations.

Subjects were asked to abstain from use of caffeine, alcohol, and scented personal products (Appendix 1) before undergoing the following tests to assess cranial nerve I, the olfactory nerve: the University of Pennsylvania Smell Identification Test (UPSIT), a 40-question scratch-and-sniff odor identification test (Doty, 1995); Amoore's odor threshold tests (Amoore and Ollman, 1983); and the Chicago Smell Test, an odor identification test (Hirsch and Cain, 1992; Hirsch and Gotway, 1993; Hirsch *et al.*, 1993).

Nerve thresholds for current perception were measured bilaterally at 2000, 250, and 5 Hz on the toes, fingers, and face (Katims *et al.*, 1986, 1987; Wesely *et al.*, 1988) to assess small-nerve fibers for peripheral nerve dysfunction. When appropriate, an R Wave to R Wave (R-R) Test (O'Brien *et al.*, 1986) of variability of electrical activity of the heart was performed to evaluate small-nerve fiber autonomic nervous system functioning.

The following electrical neurophysiologic tests were performed when indicated: prolonged latency cognitive P300 evoked responses to assess cortical function; visual evoked responses (VER) to assess cortical and optic nerve function; and somatosensory evoked responses (SSER) of all four extremities, including nerve conduction velocities to assess

peripheral-nerve function, as well as central cortical sensory connections.

In addition to standard neurologic and psychiatric examinations, subjects were given the Modified Strub and Black Mental Status Examination (Strub and Black, 1981), Trail-Making Subtest of the Halstead-Reitan Battery (Reitan, 1979), Mini-Mental-Status Examination (MMSE) (Folstein *et al.*, 1975), Millon Clinical Multiaxial Inventory – III (Millon, 1987), Minnesota Multiphasic Personality Inventory – 2 (Friedman *et al.*, 1989), Beck Depression Inventory (Beck and Beamsderfer, 1974), Zung Depression Scales (Zung, 1965), Forest Headache Questionnaire (Finstad, 1975), and Hendler Pain Test (Hendler *et al.*, 1979) to assess psychiatric versus organic origins of pain.

To rule out malingering, the following standard tests, which specifically indicate functional, nonorganic disease, were performed: test of immediate recall, i.e., reverse digit span compared with forward digit span; motor examination (the Hoover sign; Arieff *et al.*, 1961); rapid alternating movement test (paradoxical impairment); test of olfactory threshold for carbinol, a trigeminal stimulant; and the Weber localization test for cranial nerve VIII (Hendler *et al.*, 1979). The UPSIT (Doty, 1995), MMPI-2 (Friedman *et al.*, 1989), MCFI-III (Millon, 1987), and Hendler Pain Test (Hendler *et al.*, 1979) also are ancillary tests for malingering.

Whether a neurotoxin could cause asymmetric findings is problematic. Since an individual's nervous system is not pristine, unilateral findings might be manifestations of subclinical disease on one side that only becomes evident when the effects of a neurotoxin are superimposed. (Subclinical disease is an underlying state that has not become symptomatic either due to the subject's lack of self-observation, the recent onset of the problem, or the gradual presentation of the disease.) The literature is replete with such cases, e.g., unilateral carpal tunnel syndrome in response to lead exposure (Berger and Schaumburg, 1994), unilateral optic neuropathy in response to heavy metals (Cavalleri *et al.*, 1982), and so on.

In order to markedly strengthen the validity of our conclusions, we excluded unilateral findings, thereby possibly overlooking neurotoxin-caused subclinical problems.

Subjects were screened for conditions that would predispose them to neurotoxic trauma:

Potentially confounding underlying conditions

The following underlying conditions, clinical or subclinical, can predispose the nervous systems of afflicted individuals to damage with a lesser degree of neurotoxic trauma than would be required were they not so afflicted. Diabetics, for example, either have a peripheral neuropathy or are predisposed to it. If a neurotoxin causes additional peripheral neuropathy, diabetics would manifest symptoms before anyone else. An unwary examiner might attribute the symptoms to underlying diabetes without considering the added effects of the neurotoxin.

Potentially confounding conditions for autonomic neuropathy (McLeod and Tuck, 1987; Pamathier et al., 1987; Liveson, 1991; McConnell and Wilson, 1994; Polinsky and Martin, 1994)

Cancer, thyroid disease, hypertension, diabetes mellitus, renal disease, autonomic symptoms induced by medication or alcohol, cardiac disease, and family history of autonomic nervous system disease.

Potentially confounding conditions for encephalopathy (Adams and Victor, 1993)

Use of illegal drugs, certain medications (including over-the-counter), moonshine or alcohol, cardiac disease, hepatic dysfunction, renal disease, thyroid abnormalities, cancer, and family history of degenerative neurologic or psychiatric diseases.

Potentially confounding conditions for chemosensory problems (including hyposmia and hypogeusia; Hirsch, 1992)

Sinusitis, cancer, thyroid disease, hepatic disease, renal disease, use of certain medications, diabetes mellitus, and family history of chemosensory disorder.

Potentially confounding conditions for limbic encephalopathy (Lishman, 1978)

Cardiac disease, hepatic disease, renal disease, thyroid abnormalities, cancer, use of illegal drugs or certain medications, and family history of psychiatric disease.

Table 1. Physical test results

	Subject 1	Subject 2	Subject 3	Subject 4
Cranial nerves				
I UPSIT	30 (hyposmic)*	35 (normal)	35 (normal)	38 (normal)
II (with correction)	20/250 OS–20/60 OD*	20/40 OU	20/125 OU*	20/80 OD–20/50 OS
V	↓Pinprick & temp left V1*	Normal	↓Temp left V1*	Normal
Pronator drift	Mild left*	None	None	Mild left*
Dysmetria:				
Finger-to-nose	None	Slight bilateral*	None	Bilateral*
Heel-to-shin	None	Right*	None	None
Dysdiadochokinesia	Left*	None	None	Left
Holmes sign	+bilateral*	Absent	+right*	Absent
Bilateral R/L				
Brachioradialis 0+/0+*	2+–3+/2+–3+	3+/3+*	3+/3+*	
Biceps	1+/1+*	2+/2+	3+/3+*	2+/2+
Triceps	0+/0+*	1+–2/1+–2+	3+/3+*	3+/3+*
Quadriceps femoris	1+/1+*	3+/3+*	3+/3+*	3+/3+*
Ankle jerk	0+/0+*	2+/2+	3+/3+*	3+/3+*
Evoked potentials				
P300	Absent*	Absent*	Absent*	Absent*
VER	Not done	Slight delay bilat.*	Normal	Delayed on right*
SSER				
Right upper extremity/left upper extremity	Unobt/78.67*	62.93/61.87	64.51/64.51	67.54/66.45
Right lower extremity/left lower extremity	Unobt/Unobt*	30.77/29.82	37.95/30.19	Unobt/Unobt*
R-R				
+	1.091 s	0.883 s	0.824 s	1.069 s
SD	0.090 s	0.078 s	0.081 s	0.089 s

* Abnormal

Potentially confounding conditions for peripheral neuropathy (Adams and Victor, 1993)

Diabetes mellitus, renal disease, cancer, thyroid disease, use of certain medications, and family history of neurologic disease associated with peripheral neuropathy.

Potentially confounding conditions for optic neuropathy (Longstreth Jr., 1994)

Diabetes mellitus, use of certain medications or moonshine, and family history of degenerative neurologic disease including demyelinating.

Potentially confounding conditions for cephalgia (Headache Classification Committee of the International Headache Society, 1988)

International Headache Society criteria for another headache pattern.

Table 2. Cognitive test results

	Subject 1	Subject 2	Subject 3	Subject 4
Poppelreuter	Normal	Normal	Normal	Normal
MMSE	Normal	Normal	Normal	Depressed w/cog. i
Strub & Black				Impair.*
Attention	Normal	5 forward/3 backward	7 forward/3 backward*	4 forward/3 backward*
Vigilance	Normal	1 comission*	1 comission*	3 omission/2 comission*
Naming	Normal	66% parts of objects	Normal	Normal
Vocab	29%*	20%*	58%	46%*
Memory (presidents)	4*	5	3*	1*
Objects	2/5*	3/3	2/3*	1/3*
Paired association	100%	50%*	100%	50%*
Constructional ability	0%*	71%	42%*	58%
Higher cognitive function	26%*	66%	66%	60%
Proverb interpretation	40%*	60%	20%*	not done
Similarity testing	20%*	60%	60	80%
Judgment	20%*	40%*	40%*	80%
Calculation				
Verbal	62%	100%	87%	88%
Written	50%	80%	100%	50%

* Abnormal

Results

None of the subjects were diagnosed with conditions predisposing them to neurotoxic trauma and none tested positive on measures of malingering.

Tables 1 and 2 show salient results of physical and cognitive tests. Cognitive P300 evoked responses were absent in all subjects. None of the four subjects tested positive for functional problems. None had pre-existing underlying psychiatric diseases; however, as for the psychological reaction to the event, several subjects displayed elements of post-traumatic stress disorder (American Psychiatric Association, 1994). Other authors have described similar reactions following toxic exposures (Schottenfeld and Cullen, 1986). All four subjects met diagnostic criteria for H₂S-induced neuropsychiatric disorders.

Table 3 summarizes the numbers of clinical and subclinical diagnoses. Subjects averaged 5.75 clinical diagnoses (range six to eight) and one subclinical diagnosis (range zero to two).

Since H₂S can affect the neuraxis anywhere from the cortex down to the peripheral-nerve sensory receptor, for simplification we limit our discussion to the following disease states: encephalopathy; limbic encephalopathy; cephalgia; polyneuropathy; autonomic neuropathy; optic neuropathy; cranial nerve VIII neuropathy; and chemosensory dysfunction.

Diagnoses of neuropsychiatric disorders are made only if both subjective complaints and objective findings are consistent with the neuropsychiatric disorder.

Encephalopathy

Subjective complaints include at least one of the following: trouble with memory, thinking, or concentration. Supporting objective evidence includes abnormalities on the mental status part of the neurologic examination and at least one of the following: nystagmus on testing cranial nerves III, IV and VI; pronator drift on motor examination; spasticity or impaired tandem gait on gait examination; at least one abnormality on cerebellar examination; symmetric hyperreflexia on at least one reflex; and the presence of symmetric atavistic reflexes or abnormalities on ancillary tests, including at least one of the following: Strub and Black Mental Status Examination, Poppelreuter Task Test, Trail-Making Subtest of the Halstead-Reitan Battery, MMSE, or CNS components of neurophysiologic evaluations of EEG, fast Fourier transform (FFT) analysis, P300, VER, brainstem auditory evoked response (BAER) or SSER.

Limbic encephalopathy

By definition, limbic encephalopathy is an abnormality of the limbic system (emotional brain) due not to psychological distress but to direct organic impact. It is the emotional equivalent of a dominant-hemisphere stroke causing aphasia or a parietal-lobe seizure causing sensory phenomena. In this instance, the limbic system problems are due to H₂S-induced organic brain damage of the limbic lobe, causing psychiatric and psychological manifestations. The presence of limbic encephalopathy does not exclude the possibility of additional

Table 3. Diagnoses

	Subject 1	Subject 2	Subject 3	Subject 4
Encephalopathy	Subclinical	Clinical	Clinical	Clinical
Limbic encephalopathy	–	Clinical	–	Clinical
Cephalgia	–	–	Clinical	Clinical
Chemosensory Dysfunction	Hyposmia Subj. hypogeusia	Subj. hyposmia Phantosmia Hypogeusia Phantogeusia	Subj. hyperosmia	Subj. hyposmia Hypogeusia
Optic neuropathy	–	–	Clinical	–
Autonomic neuropathy	Clinical	Clinical	Clinical	Subclinical
Polyneuropathy	Subclinical	Subclinical	–	Clinical
Cranial nerve VIII neuropathy	–	Clinical	Clinical	–
Total diagnoses	3	8	6	6
Subclinical	2	1	0	1

psychological reactions to the illness, but the diagnosis addresses organic damage to the area of the brain that creates emotions.

Subjective complaints include trouble with emotions, depression, sadness, crying spells, decreased energy, decreased sex drive, and easy fatigability. Objective evidence includes at least one of the following on neurologic examination: mental status abnormality; nystagmus on cranial nerves III, IV and VI testing; pronator drift on drift testing; spastic gait or unstable tandem gait; abnormal cerebellar function in at least one test bilaterally; hyperreflexia with 3 or 4+ reflexes bilaterally at at least one site; and at least one bilateral atavistic reflex. If no neurologic abnormalities are present, there must be at least one abnormality on ancillary tests including modified Strub and Black Mental Status Examination, Poppelreuter Task Test, Trail-Making Subtest of the Halstead-Reitan Battery, the MMSE, or electrophysiologic abnormalities on P300 or EEG with FFT analysis.

Cephalgia

Criteria for a diagnosis of H₂S-induced cephalgia are marked exacerbation in severity and/or duration of an underlying headache pattern or development of a new headache pattern in the absence of other known causes. For a new headache to meet criteria for neurotoxin-induced cephalgia, it must not meet criteria for any common headache syndrome described in the Forest Headache Questionnaire (Finstad, 1975) or the International Headache Society (Headache Classification Committee, 1988), and must be severe enough to bother the subject. Further, the headache must have begun at the time of exposure or soon thereafter and persisted until the examination.

Polyneuropathy

Subjective complaints include either numbness or weakness in the arms or legs. Objective findings include at least one of the following: on motor examination, atrophy, symmetric reduction in strength, bilateral pronator drift; on gait examination, bilateral foot drop or inability to heel-to-toe walk; on the sensory examination, bilateral abnormality; on the reflex examination, bilateral hyporeflexia. Or, in addition to subjective com-

plaints, at least one of the following ancillary tests must be abnormal: bilateral nerve threshold measurements, R-R Test, or bilateral nerve conduction velocities.

Autonomic neuropathy

Complaints include consistent nonvertiginous light-headedness and impotence. Objective physical findings are the same as for polyneuropathy.

Optic neuropathy

Complaints are trouble with vision, including blurred vision not related to need of glasses. Objective physical findings include abnormalities on the cranial nerve II examination, visual acuity greater than 20/60 OU with correction, presence of Marcus-Gunn pupil, optic atrophy or optic neuritis as demonstrated on funduscope or by visual field deficit on direct confrontation and opticokinetic nystagmus test. Abnormalities on ancillary tests consistent with H₂S-induced optic neuropathy include VER.

Cranial nerve VIII neuropathy

Complaints include trouble with hearing or tinnitus. Objective evidence includes at least one of the following: nystagmus on extraocular muscle test; impaired hearing; abnormal Weber or abnormal Rhinne test; or abnormal BAER.

Chemosensory dysfunction

Complaints include difficulty in smelling or tasting. Objective evidence includes abnormal UPSIT scores. None of the subjects had diseases that would account for chemosensory dysfunction.

Subclinical diagnoses

Subclinical diagnoses are defined as the presence on physical examination and associated tests of abnormalities without related subjective complaints. For example, an areflexic individual who has no complaints consistent with a polyneuropathy would be given a subclinical diagnosis.

Discussion

This is the first documentation of abnormal P300 and chronic sequelae due to H₂S exposure without loss of consciousness.

The nervous system and its end organs, prime targets for toxins because of their fragile nature, readily manifest any disturbances.

Neurotoxins not only occupy our landfills and dumpsites, they pollute our waters and even infiltrate the food chain. Trichloroethylene, arsenic, and PCBs are only a few neurotoxins whose contamination has reached virtually epidemic proportions (Franzblau, 1994; Tilson and Garry, 1994). They affect the CNS and the peripheral nervous system as well and tend to cause cranial nerve dysfunction. Typically they cause cephalgia, encephalopathy, limbic encephalopathy, cranial neuropathies, polyneuropathies, and autonomic neuropathies, indicating that the nervous system responds in essentially similar ways to various neurotoxins. Dysfunction manifests at the site of the weakest link in the physiologic chain (*locus minoris resistentiae*); where subclinical pathology already exists, homeostasis fails. This, we suggest, accounts for individual variation in neuroanatomical and clinical presentation.

Neurotoxins such as H₂S, trichloroethylene, lead, and arsenic all pass through the blood–brain barrier. The brain, limited in its responses, can manifest abnormal behavior as a positive symptom (seizure), a negative symptom (paralysis), or something in between. Commonly, exposure to neurotoxins reduces a subject's maximal capabilities as they existed prior to exposure; cognitive abilities of intelligent persons may still be superior after exposure, but less so. Similarly, a peripheral-nerve conduction in the high-normal range may remain normal after exposure, but low-normal. In this study, we diagnosed H₂S-induced abnormalities conservatively by assuming the absence of any supernormal pre-exposure abilities. We scored all characteristics as normal when test results were within the normal range even if subjects complained to the contrary.

When subjective complaints and objective neurologic signs are at odds, neurotoxicity is difficult to diagnose. In subjects with symptoms but no confirmatory objective evidence, we have a diagnostic

dilemma. Are their symptoms the disingenuous complaints of malingerers or the neurotic ravings of hysterics? Or do they accurately represent subjective feelings due either to dysfunctions so subtle we cannot measure them, or to pre-existing complaints that, had the subjects been interviewed prior to the toxic exposure, would be shown on neurologic histories? We can hope to answer these questions by performing tests for malingering (Hunt, 1973) and reviewing old records. Results of examinations to detect malingering and hypochondriasis were negative for all our subjects. And all of their complaints seemed justified according to test scores.

At the opposite end of the spectrum are subjects who show objective neurologic deficits on physical examination but have no subjective complaints. Are these individuals H₂S-damaged but unobservant? Are they in a subclinical disease state and predisposed to neural disease by a weak link in the homeostatic chain so that it is merely a matter of time before symptoms become manifest? Such individuals, with their less healthy neurologic reserves, are more likely to manifest disease states as their nervous systems degenerate, e.g., with aging or trauma (Houx and Jolles, 1994; Longstreth Jr., 1994). In neurotoxicology, the subclinical state is called 'coasting.'

In the absence of pre-exposure data, the question arises as to whether subclinical disease was present prior to the toxic exposure (Berger *et al.*, 1992). Among our subjects, however, the similarities of their objective findings seem to indicate an H₂S-induced origin. The absence of abnormalities on previous medical records, the relative youth of the subjects, and the fact that they were actively employed at the time of exposure weigh against the presence of prior deficits. Presumably, if they had significant deficits, they would not have sufficiently advanced in their occupations to be employed by this prestigious, sought-after employer. Our pre-exposure history of function and objective tests was designed to ferret out any pre-existing neurotoxic disease. Scores of recent and remote function did not differ for any subjects, indicating that their problems were new, toxin related.

As in any epidemiologic study, various potentials exist for bias (Wiggins and Brandt, 1988; Less-Haley and Brown, 1992). That all subjects were self-

selected is a bias since people with problems would be more interested in being evaluated than would persons without problems. Furthermore, their lawsuit against the employer might prompt them to emphasize their symptoms for purposes of the litigation. We attempted to minimize such bias by testing everyone individually without others of the group present and questions were phrased in a neutral fashion.

Our stringent definition of abnormality on physical examinations and our requirement of symmetrical involvement yield results that underestimate the severity as well as frequency of disease. Despite this, the extent of H₂S-induced neurologic disease shown by these four individuals is extraordinary.

The pathophysiology of H₂S in our subjects remains speculative. The traditional assumption of H₂S-induced respiratory arrest with subsequent anoxic injury does not apply. A more tenable mechanism may be the inhibition of cytochrome oxidase in the Krebs's cycle in mitochondria, through depleting cellular energy (Stene *et al.*, 1976; Kangas *et al.*, 1984; Arnold *et al.*, 1985; Gaitonde and Sellar, 1987; Bhambhani and Singh, 1991). Alternatively, H₂S may interfere with neuronal metabolism by binding the disulfide bridges in proteins to form persulfides (Warenycia *et al.*, 1990; Kilburn and Warshaw, 1995a). In either case, the toxin would be absorbed from the lungs into the blood and across the blood–brain barrier (Haggard, 1925; Beauchamp *et al.*, 1984; Warenycia *et al.*, 1990).

Aspects of our findings deserve further amplification. All subjects displayed persistent sequelae of encephalopathy. Since H₂S is used throughout industry and chemical plants often abut residential sites, this neurotoxin has become ubiquitous in our communities. An ever-growing population is at risk of an epidemic of chronic low-level H₂S poisoning (Beliles and Beliles, 1993; Kilburn and Warshaw, 1995a).

Why has a high level of encephalopathy among H₂S workers not already been reported? Perhaps it has been observed but either employers ignore it, or the encephalopathy is misdiagnosed as neurasthenia. Sophisticated neuropsychiatric tests have only recently become available to delineate these sequelae – the abnormal P300 due to H₂S in the absence

of abnormal neurologic examination (Folstein *et al.*, 1975). Also, patients tend not to complain and even ignore subtle, slowly developing deficits, especially in the cognitive realm.

Could something unique about our subjects have predisposed them to the neurotoxicity of H₂S? Histories of exposure to lead, H₂S, and sometimes other chemicals that could have acted synergistically may have induced a deficit as has been described with other neurotoxins (Kilburn and Warshaw, 1995a). Recurrent H₂S exposure may induce hypersensitivity to future exposures (Adelson and Sunshine, 1966; Bolla-Wilson *et al.*, 1988; Klaassen, 1993).

All our subjects used alcohol, and since acute alcohol ingestion may reduce olfactory ability, hence reduce detection of the odor of H₂S, these subjects may have remained longer at higher H₂S concentrations than would individuals who do not use alcohol (Hirsch and Bussell, 1995). And alcohol may directly affect the nervous system making the individual more susceptible. The implications are grave. Eight per cent of the work force in the USA, the group at highest risk for H₂S exposure, have disorders related to alcohol use.

All four of our subjects displayed chemosensory disorders. The mechanism of H₂S-induced chemosensory loss includes hematogenous spread across the blood–brain barrier, but H₂S may also act directly on the epithelium at the olfactory cleft, overwhelming nasal xenobiotic metabolism with possible transneuronal distribution through the olfactory bulb and tract and into the limbic system. The same transneuronal transfer has been postulated to occur with aluminosilicates in senile dementia of the Alzheimer's type, as well as with some forms of encephalitis.

Perhaps H₂S was not present at steady low concentrations but intermittently at higher concentrations, which were not high enough to induce loss of consciousness. Either way, our subjects were exposed to relatively low doses.

Chronic effects of exposure to even relatively low concentrations must now be considered a potential health hazard not only to occupational workers but even to the general population, since the industrial uses of H₂S are ubiquitous.

The high incidence of chronic neuropsychiatric sequelae in our four subjects indicates that a

rigorous epidemiologic study of persons who work with H₂S should be undertaken.

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Appendix I

Since we are testing abnormalities of smell and taste, the following precautions must be taken:

- You may consume no caffeine for at least 48 hours prior to your visit. (Below is a list of foods and beverages containing caffeine.)
- You may drink no alcohol for at least four days prior to your visit.
- You may eat no pastries for 24 hours prior to your visit.
- From midnight on, until your visit, you may have none of the following: food; gum; cigarettes; or any drink other than water.

IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS TO INSURE THE VALIDITY OF THESE TESTS.

- From midnight before the day of your test, you should use no scented soap, cosmetics, deodorants, shaving cream, after shave, perfumes or lipsticks. The only underarm deodorant you may use is Gillette roll-on.
- From midnight before your visit, you may use only shampoo with no (or minimal) smell, e.g., Ivory shampoo.
- You may brush your teeth, but we ask that you not use toothpaste.
- All prescribed medications should be taken and those clients with diabetes should eat.

FOODS AND BEVERAGES CONTAINING CAFFEINE THAT YOU SHOULD TRY TO AVOID FOR 48 HOURS BEFORE TESTING:

- Chocolate
- Coffee
- Decaffeinated coffee
- Colas
- Tea
- Cocoa
- NoDoz
- Other over-the-counter products that are stimulants

BE SURE TO READ YOUR LABELS

