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Absence of toxic effects in silver reclamation workers

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PIFER JW, FRIEDLANDER BR, KINTZ RT, STOCKDALE DK. Absence of toxic effects in silver reclamation workers. *Scand J Work Environ Health* 1989;15:210–221. Recent reports have alleged that silver presents a toxic hazard to exposed workers. To define the potential risks of long-term exposure to silver better, a cross-sectional investigation was conducted of 27 Caucasian males occupationally exposed to primarily insoluble silver compounds and 27 matched referents. Physical examination and electron microscopy of skin biopsies revealed no cases of generalized argyria. Measurements of facial discoloration, judged from color photographs by panels of laymen and physicians, showed no significant difference between the two groups. Although 29 % of the silver workers and none of the referents exhibited ocular silver deposition, optometric and contrast sensitivity test results revealed no significant deficits in visual performance. The kidney and respiratory findings were essentially normal in both populations. Despite the increased presence of silver in the blood, feces, and hair of the recovery workers versus the referents, there was no evidence that chronic silver exposure adversely affected the health of these employees.

Key terms: argyria, argyrosis, biological monitoring, clinical study, contrast sensitivity, epidemiologic study, insoluble silver compound, occupational silver exposure.

From an occupational health standpoint, interest in the dermatologic effects of silver (argyria) has lessened considerably during the past few decades as changes in manufacturing processes and improved industrial hygiene practices have significantly reduced workplace exposures. Toxicologic evidence has generally supported the clinical observation that chronic exposure to metallic silver and its soluble salts (and presumably insoluble compounds) does not appear to represent a serious health risk to man. However, health data from clinical studies in the United States (1–3), and case histories reported in the European literature during the past 15 years (4–15) have suggested the need to reevaluate the human toxicologic effects of silver for such target organs as the skin, eyes, lungs, and kidneys. In addition, it is important to define more precisely the potential risks of long-term exposure to insoluble forms of silver, which have been incompletely studied and for which there is no workplace standard in the United States (US).

This paper describes air sampling results and clinical and epidemiologic findings for a group of silver reclamation employees and their matched referents at a large photographic manufacturing facility. Specific study objectives included investigations of (i) argyria (localized and generalized), (ii) argyrosis (ocular sil-

ver deposition), (iii) visual contrast sensitivity, (iv) respiratory symptoms and diseases (pulmonary function and chest radiographs), and (v) renal function (clinical laboratory studies). To augment the determinations of the airborne silver levels, biological monitoring was also performed.

Subjects and methods

Silver recovery operations and air sampling data

The silver recovery department of the plant in question, which operates on a full-time basis (24 h/d, 365 d/year), is responsible for the reclamation of silver from photographic film, paper, and liquid wastes. It also reclaims cellulose acetate from scrap film. Table 1 describes the major occupations in the department and provides estimates of their relative silver exposure levels.

Chemical analyses of factory dusts by serial dissolution with distilled water followed by the addition of dilute nitric acid have indicated that greater than 90 % of the silver is present as water- and acid-insoluble halides, principally silver bromide; the remainder consists primarily of silver oxide, silver sulfide, or metallic silver. Only trace amounts of soluble silver compounds such as silver nitrate have been detected.

The American Conference of Governmental Industrial Hygienists (ACGIH) has established threshold limit values (TLV®) for metallic silver and soluble silver compounds (undefined). Whereas an 8-h time-weighted average (TWA) exposure of 10 µg Ag/m³ had been originally established for both the metal and soluble compounds, in 1980 a TLV of 100 µg/m³ was adopted for the metal (16), and in 1981 the 10 µg Ag/m³ level was reaffirmed for soluble compounds

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(17). In 1971 the US Occupational Safety and Health Administration (OSHA) established a standard of 10 $\mu\text{g Ag/m}^3$ for both silver metal and its soluble compounds (18). Finland and the United Kingdom have promulgated standards of 10 $\mu\text{g Ag/m}^3$ and 100 $\mu\text{g Ag/m}^3$, respectively, for soluble and insoluble forms of silver (19).

The estimates of the potential annual average for personal exposure rates (8-h basis) shown in table 1 were determined from an analysis of more than 100 area and personal (breathing zone) samples collected since the mid-1950s. Samples of airborne dust were collected on mixed cellulose ester filters and analyzed by either atomic absorption spectrophotometry or inductively coupled plasma atomic emission spectrophotometry. Silver exposures in this environment are highly variable due to the extreme values (thousands of micrograms per cubic meter) which may occur for limited periods during cleaning and maintenance operations and during nonroutine events such as equipment malfunctions. In the determination of annual occupational exposure rates, the average of full-shift sampling data for an occupation was increased on the basis of an estimate of the frequency of irregular, short-term, high-exposure tasks. Historically, the number and severity of such exposures have varied with the introduction of new procedures, often compounded by equipment problems. Because of individual work practices, including the use of respiratory and facial protection, and differences in occupational assignments, actual personal exposures may have differed from the values in table 1, which should be considered as approximations of chronic silver exposure.

Subjects

Thirty-one men with five or more years of experience (by 1979) in those areas with the highest potential for exposure were eligible to participate in the study. Included were burner operators, maintenance workers, mechanics, and smeltery and centrifuge operators; four employees were supervisors. Because of the difficulty in diagnosing argyria, three nonwhites were excluded from the analysis, although they were given standard clinical examinations, including laboratory studies. In addition, one worker chose not to participate. The final exposed group, therefore, included 27 Caucasian men.

An equal number of employees, matched with the exposed subjects by age (5-year category), sex (male), and race (Caucasian), were randomly sampled from one manufacturing ($N=11$) and two office ($N=16$) departments in which silver was not used. None of the referents had an occupational history of silver exposure. Since participation in the study was voluntary, provision was made for the random selection of alternates.

Using the same criteria, a physician and an occupational health nurse shared responsibility for examining the study subjects during February–April 1979. Optometric examinations were conducted in January 1981. The clinicians were blinded as to the employee's occupational status (exposed or reference subject).

Health questionnaire

The subjects completed a brief, self-administered medical history form which requested information about

Table 1. Major silver recovery occupations and annual 8-h exposure rate estimates.

Occupation	Description	Number of samples ^a	Estimated annual exposure rate ($\mu\text{g Ag/m}^3$) ^b
Smelter and refining operator	Loads smeltery with ashes from incinerator, manually rakes molten charge, and taps smeltery to collect liquid silver and slag	39	200
Incinerator operator	Burns waste photographic paper and film to produce silver-containing ash	45	190
Maintenance operator	Repairs smelteries, incinerators, and process machinery	4	150
Water treatment operator	Directs treatment of silver-rich waste waters, including roasting of sludge to remove water and volatile organic matter	2	40
Metal purging operator	Fills tank with ashes and dusts collected in air pollution control equipment	9	30
Materials handler	Operates forklift truck used to transport waste film and chemicals	2	20
Washer operator	Supervises film washing process	2	10
Drier operator	Oversees drying and fine chopping of waste film for acetate recovery	2	10
Office worker	Inventories materials, performs engineering services, supervises employees, etc	..	5

^a Area samples and personal dosimetry, 1953–1986.

^b Eight-hour basis, unadjusted for the use of respiratory or facial protection.

smoking habits, alcohol consumption, medication usage, and respiratory symptoms and illnesses.

Physical examination

In addition to height, weight, and blood pressure measurements, the clinicians examined each employee's face, neck, nasal and oral mucosa, and gums for signs of argyria.

Facial photograph study

The objective of the facial photograph study was to determine whether the silver workers had more facial discoloration than their matched referents and, if so, whether it was judged to be cosmetically objectionable. Panels of laymen and physicians evaluated color photographs of the faces of each matched pair of study subjects for the presence of skin discoloration. The portrait judged to have the most pigmentation was rated according to the degree of cosmetic objectionability. (A description of the study methods is included in the appendix.)

Electron microscopy

The subjects included five randomly selected silver workers with an average of more than 29 years of recovery experience and two referents. Skin biopsies from the buttock region were assessed for the presence of silver by microscopic X-ray diffraction analysis. (The laboratory techniques are discussed in the appendix.)

Ophthalmologic studies

Twenty-four silver workers and 22 referents were evaluated in 1981 by an experienced optometrist. Each was given a standard optometric evaluation, including visual acuity (uncorrected and corrected), Schiötz tonometry, keratometric reading, and an ophthalmoscopic examination of the fundi. The data were analyzed separately for the right and left eyes, and in the case of visual acuity also for binocular viewing. In addition, conjunctival pigmentation was graded by direct visualization, while the cornea and lens were examined by slit-lamp biomicroscopy. As has already been indicated, all the studies were conducted without knowledge of the employee's occupation.

Contrast sensitivity experiment

Contrast sensitivity is a measure of the eye-brain capacity to detect luminance contrast at various spatial frequencies. It is determined by changing the contrast (light-dark difference) of a spatial sine wave target around a threshold level at a selected frequency until an image is perceived P % of the time. Performed in conjunction with standard visual acuity testing, this technique offers potential value in diagnosing ocular impairment in a wide range of clinical situations (20—22).

During 1981, an experiment was conducted to test the hypothesis that the deposition of metallic silver in the cornea might act to scatter incoming light in the ocular media and thereby cause a retinal image of reduced contrast, particularly under veiled glare conditions (23, 24). Specifically, if silver deposition were responsible for a significant degree of retinal contrast loss, the recovery workers would be expected to exhibit lower contrast sensitivities than the referents. Furthermore, it was hypothesized that these values would be differentially reduced under conditions of glare illumination.

Of the 54 individuals originally studied, three silver workers and five referents chose not to participate, and thus the exposed and reference groups were reduced to 24 and 22 subjects, respectively. Briefly, the study was conducted as follows. A projected image of light and dark vertical bars was viewed through a translucent diffusion screen which, depending on the subject's response, was moved closer to or away from the stimulus until a final threshold level was achieved. The number of "counts" (steps separating the image from the diffusion medium) was analyzed for the silver workers with and without corneal deposition and for the referents according to various spatial frequency and illumination parameters. The subjects with a large number of "counts" were considered to have a low contrast pattern and high sensitivity. (The study methodology, including a schematic diagram of the instrumentation, is presented in the appendix.)

Pulmonary function

Measurements of age- and height-adjusted forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_{1.0}) were calculated on the basis of regression equations derived from a random sample of "healthy" white, nonsmoking males 25 years of age and older (25). To assess the statistical significance of silver exposure and smoking effects (including their interaction), a two-way analysis of variance (ANOVA) was performed.

Chest radiography

Posterior-anterior and lateral chest radiographs were evaluated by a radiologic consultant.

Clinical laboratory studies

For the evaluation of renal function, estimated creatinine clearance, based on the median of three 40-min timed urine collections, and serum creatinine tests were undertaken. The creatinine clearance values were corrected for lean body mass with the use of a body surface area nomogram (26). Regression analysis techniques were used to assess the relationship with estimated career silver exposure. Four liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase) were also measured. Other tests included blood

urea nitrogen, total cholesterol, complete blood count, and urinalysis.

Biological monitoring

A study was conducted to estimate the body burden of silver in the recovery workers, including the amount absorbed and excreted in selected biological specimens, and to compare these data with similar information for their matched referents. Samples of blood, urine, feces, and hair were analyzed for total silver by flameless atomic absorption spectroscopy. The methodology and results of a larger study of silver recovery workers and referents have been published earlier (27).

Results

Age and employment history

The average age of the 27 silver workers in 1979 was 46.2 years. Historically, employment in the department has been stable. Nine subjects had at least 30 years of experience, while six had worked for less than a decade. The mean duration of employment was 19.3 (range 6–39) years. The referents' average age was 45.6 years, and their average tenure 20.4 years.

Height, weight, and blood pressure

The silver workers weighed an average of approximately 9 kg more than their matched referents (91 versus 82 kg, $P < 0.05$). Thirty-seven percent and 11 % of the recovery employees and referents, respectively, were at least 20 % above their mean age- and height-specific weight (28). Elevated blood pressures [systolic ≥ 140 mm Hg (18.62 kPa) and/or diastolic ≥ 90 mm Hg (11.97 kPa)] were reported for approximately one-third of the employees in each group.

Dermatological findings

No cases of generalized argyria were observed. Twenty of the 27 silver workers (74 %) exhibited some degree of internal nasal-septal pigmentation, almost half displaying "trace" amounts; three had "marked" discoloration. In contrast, no nasal staining was observed in the referents. Examinations of the oral mucosa, gums, and face showed no staining in either group of employees.

Facial photograph study

Neither the physicians nor the laymen were able to distinguish the exposed subjects from the referents at rates significantly different from chance. The medical judges selected silver workers 54 % of the time ($P = 0.10$) compared with 53 % for the laymen ($P = 0.16$). In addition the mean pairwise differences in the discoloration scores between each exposed subject and his matched referent were not significantly different from zero. The laymen reported substantially more "obvious" pigmentation (8.3 % of the silver workers and 11.5 %

of the referents) than the physicians (0.0 and 0.8 %, respectively). In addition, no statistically significant differences between the silver workers and the referents were found when the ANOVA was performed, regardless of the panel composition. The P -values for the physicians alone and for all three panels (clinical physicians, research physicians, and laymen) were 0.63 and 0.87, respectively.

Electron microscopy

Examination of the granular and basement membrane structures and of the staining pattern of collagen revealed no evidence of silver in any of the biopsy specimens.

Ophthalmologic examination

The most noteworthy ocular manifestation was argyrosis, a staining of the bulbar conjunctiva and its contiguous mucosal surfaces. Compared with the reference group, in which no unusual findings were reported, five of the 24 (21 %) silver workers had grade 1+ or higher conjunctival discoloration, while six (25 %) had corneal silver deposition detectable in Descemet's membrane (table 2).

Overall, seven (29 %) employees showed some degree of pigmentation in one or both eyes (table 3). Conjunctival staining only was observed in one worker, while two had barely detectable amounts of corneal pigmentation only. The individual with 3+ conjunctival and 2+ corneal deposition had been employed in the recovery department for approximately 32 years, 15 of which were in materials handling and washing operations, 11 in water treatment, 5 in smelting/refining, and 1 in incinerator operations. His estimated career exposure (see definition given later in the text) was in excess of 2 000 ($\mu\text{g Ag/m}^3$)-years. None of the subjects, including the referents, exhibited lens changes or funduscopy abnormalities.

Table 2. Grade of argyrosis in conjunctiva and cornea of silver workers.

Silver deposition grade ^a	Conjunctiva		Cornea	
	N	%	N	%
0	19	79.2	18	75.0
1+	2	8.3	4	16.7
2+	2	8.3	2	8.3
3+	1	4.2	—	—
Total	24	100.0	24	100.0

^a Ocular silver deposition was graded as follows: conjunctiva (no slit lamp): 0 = not present or trace amount, 1+ = barely detectable at one foot (approximately 30.5 cm) or limited to caruncle, 2+ = easily detectable at one foot (approximately 30.5 cm) or evident in nasal quadrants of bulbar conjunctiva, 3+ = easily detectable at four feet (approximately 122 cm) or evident in both nasal and temporal quadrants; cornea (slit lamp): 0 = not present, 1+ = barely detectable in Descemet's membrane, 2+ = easily detectable in Descemet's membrane.

Table 3. Argyrosis in silver workers by estimated career silver exposure.

Estimated career silver exposure ^a ($\mu\text{g Ag/m}^3$)-years	Site of argyrosis				Highest grade of argyrosis, all sites ^b			Total positive cases	
	None	Conjunctiva	Cornea	Conjunctiva and cornea	1+	2+	3+	N	%
< 1 400	7	—	—	1	—	1	—	1/8	13
1 400—2 100	7	1	—	1	1	—	1	2/9	22
> 2 100	3	—	2	2	3	1	—	4/7	57
Total	17	1	2	4	4	2	1	7/24	29

^a Unadjusted for the use of respiratory or facial protection.^b See table 2 for an explanation of the grades.

A dose-response analysis was conducted based on exposure estimates derived from the historical job history data, including those from both the questionnaire and personal interview. Work assignments in the silver recovery department (through January 1981) were assessed according to the duration (months) and estimated level (micrograms of silver per cubic meter) of exposure. The accumulated product, an estimate of potential career silver dose, was expressed in units of micrograms of silver per cubic meter-years [$(\mu\text{g Ag/m}^3)$ -years]. The study population was divided into three dosage groups of approximately equal size, the natural separations in the exposure distribution being taken into consideration. The summary statistics were as follows: mean career exposure rate 110 (range 5—240) $\mu\text{g Ag/m}^3$ and mean career dose 1 900 (range 70—7 000) $(\mu\text{g Ag/m}^3)$ -years.

An evaluation of the argyrosis cases according to estimated career exposure category (table 3) suggested a dose-response relationship ($P=0.06$, chi-square test for linear trend). Further analysis using individual career exposure values indicated that the regression coefficient was significantly different from zero ($P=0.03$, chi-square test).

To determine whether silver deposition was associated with ocular impairment, we divided the exposed subjects into two groups according to the presence ($N=6$) or absence ($N=18$) of corneal silver deposition; data for the referents were also analyzed. On the basis of Student's *t*-test, no significant differences were found between the two populations of recovery employees or between the silver workers and the referents for any of the standard optometric tests evaluated (refractive error, keratometry, tonometry, and corrected visual acuity).

Visual contrast sensitivity experiment

A comparison of the "counts" with a two-sample *t*-test indicated that there were no significant differences between the silver workers and the referents at any of the frequency/glare levels ($P=0.14$ to 0.96). In general, the contrast sensitivity measurements were higher for nonglare illumination. Contrary to the hypothesis relating lower contrast sensitivity with argyrosis, workers with corneal silver deposition demon-

strated consistently higher values than those with no ocular pigmentation. However, the differences between the two groups were not statistically significant ($P=0.06$ to 0.90).

Respiratory system findings

Symptoms. On the questionnaire four silver workers and two referents reported that they were "troubled with a cough almost every day." One recovery employee, a nonsmoker with recurrent respiratory infections, became asymptomatic following antibiotic therapy. Another, who had smoked a pack of cigarettes daily for 10 years, had symptoms consistent with a diagnosis of chronic bronchitis. The third was a long-term smoker (31 pack-years), while the fourth had never smoked cigarettes. All had negative radiographic findings; none had a history of asthma or wheezing.

One referent with a 68 pack-year smoking history indicated that he had had a chronic cough of more than six month's duration during each of the past two to four years; his chest radiograph was "suggestive of mild chronic bronchitis." The other, an ex-smoker, had smoked 1.5 packs of cigarettes per day for 30 years.

Pulmonary function. No significant differences in ventilatory performance were observed between the study groups according to smoking category. The mean FVC values of 4.5 and 4.6 l ($P=0.16$) for the silver workers and referents, respectively, and the mean $\text{FEV}_{1.0}$ of 3.6 l for both groups ($P=0.39$) were not statistically different. The majority of employees with spirometric abnormalities were chronic tobacco users (30—45 pack-years). Four of the five silver workers and five of the six referents with a decreased $\text{FEV}_1\%$ [$(100 \times \text{FEV}_{1.0}/\text{FVC})$ ($<75\%$)] were smokers.

Chest radiograph. No abnormalities were observed among the recovery employees, while the one referent with symptoms suggestive of bronchitis was reported to have "mild accentuation of bronchovascular markings in both lung fields." A stable granulomatous lesion was also observed in a silver worker.

Clinical laboratory data

Urinary system findings. The mean creatinine clearances of 0.98 and $1.10 \text{ ml} \cdot \text{s}^{-1} \cdot \text{m}^{-2}$ for the exposed and reference groups, respectively, were not significantly different ($P=0.10$, paired t-test). One silver worker with a history of chronic alcohol abuse had an abnormally low value ($0.28 \text{ ml} \cdot \text{s}^{-1} \cdot \text{m}^{-2}$). None of the referents had an abnormal creatinine clearance level. An analysis of dose response showed no significant relationship between career silver exposure and creatinine clearance ($P=0.31$). The mean serum creatinine values for the exposed workers and the referents were, respectively, 92 and $87 \text{ } \mu\text{mol/l}$ ($P=0.14$), while the mean blood urea nitrogen level of 6.2 mmol/l of the referents was marginally higher than that of the silver workers (5.4 mmol/l) ($P=0.07$). The urinalysis results for protein, glucose, and both red and white blood cells were not statistically different in the two populations.

Other clinical laboratory results. None of the differences in liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase) between the exposed workers and the referents was of statistical significance. The exposed workers exhibited a marginal decrease in red blood cell count (5.1 versus $4.9 \cdot 10^6$, $P=0.04$), and a significant increase in mean corpuscular volume (94.7 versus $90.0 \text{ } \mu\text{m}^3$, $P=0.02$); neither finding was considered clinically important.

Biological monitoring. The mean concentration of silver was $0.010 \text{ } \mu\text{g/ml}$ among the 21 reclamation employees with measurable blood silver levels ($\geq 0.005 \text{ } \mu\text{g/ml}$). In contrast, silver was not detected in the blood of any of the referents. Detectable levels of urinary silver ($\geq 0.005 \text{ } \mu\text{g/g}$) were observed in only one exposed worker who had normal renal function and in none of the referents. Silver was observed in all fecal samples collected with mean concentrations of 16.8 and $1.5 \text{ } \mu\text{g/g}$ for 18 exposed workers and 22 referents, respectively ($P<0.01$). The mean silver concentration in the washed hair samples was markedly higher ($P<0.01$) in the exposed group ($88 \text{ } \mu\text{g/g}$, $N=26$) than in the reference group ($0.5 \text{ } \mu\text{g/g}$, $N=27$). However, this difference may have reflected the potential direct binding of airborne silver particles to the hair rather than its metabolic deposition.

Discussion

This investigation has demonstrated no unusual health patterns in 27 employees with long-term exposure to primarily insoluble silver compounds. On the basis of the findings of reports involving soluble compounds, the following four hypothesized target organs were examined: skin, eyes, lungs, and kidneys.

The principal forms of silver discussed in the literature have been soluble compounds, notably silver nitrate. The health risks associated with exposure to

insoluble compounds such as silver halide have been less extensively addressed. Data from nonmammalian studies have shown that the toxicity of silver differs substantially depending upon its speciation. LaBlanc et al (29) reported that relatively insoluble compounds, such as silver sulfide and silver thiosulfate complexes, are approximately 15 000 times less acutely toxic to fathead minnows than silver in its soluble state (free silver ion). While it is difficult to extrapolate human toxicity potential from investigations of aquatic life, the results demonstrate the need to consider silver speciation in the assessment of human health effects.

Historically, the primary chronic health concern associated with silver has been its skin effects. Electron microscopic studies have determined that silver granules are deposited primarily in the basal lamina of the eccrine sweat glands, in the dermal elastic fibers, and around pilosebaceous structures (10). While a melanin-silver interaction has been suggested (30), silver is more commonly found in nonmelanin-containing tissue (10, 31). Such deposition, which causes the slate-gray appearance characteristic of generalized argyria, has not responded satisfactorily to depigmentary therapeutic agents, including potassium iodide (32), methenamine (33), and sodium thiosulfate (34).

Case reports and clinical studies describing argyria (both local and systemic) and argyrosis have been reported for persons with a history of occupational silver exposure (1–3, 5, 10, 35–37). Occupational epidemiologic studies using matched, unexposed referents have not been reported in the literature.

The earliest documented case of work-related argyria, published in 1872 (38), occurred in a 72-year-old French woman with 50 years of experience as a silver polisher. Case series by Harker & Hunter (35) in 1935 and Hill & Pillsbury (36) in 1939 described localized argyria in 11 workers (silversmiths, polishers, smelters) exposed primarily to silver metal particles and generalized argyria in 17 individuals (silver nitrate makers and packers, engravers, miners) with industrial exposure to silver compounds (table 4).

In 1958, Remler (37) reported 31 cases of occupational argyrosis in employees exposed 2–30 years to silver bromide and silver nitrate in the manufacture of photographic and X-ray films. In this study, the cases demonstrated no decrement in visual acuity, field of vision, or color perception. It was hypothesized that argyrosis originates from the external deposition of insoluble silver granules in the conjunctival sac. Once deposited, a chemical reduction to the metal occurs through the combined effects of vitamin C-rich alkaline tears and ultraviolet light.

A 1979 cross-sectional clinical investigation of 30 workers exposed to silver nitrate and silver oxide indicated that six were diagnosed with generalized argyria and 20 with argyrosis (1). A later study by the same author (3) found 10 cases of conjunctival ($\geq 2+$) and six cases of corneal ($4+$) argyrosis in 27 workers exposed to a variety of silver compounds (nitrate,

Table 4. Selected studies of the health effects of occupational silver exposure, 1935–1987. (NA = not ascertained)

Reference	Type of study	Sample size	Exposure data ^a			Skin		Eyes	
			Compound	Speciation	Occupation	Localized argyria	Generalized argyria	Argyrosis	Visual impairment
Harker & Hunter (35)	Case series	16	Silver fulminate, silver nitrate, and silver metal	Insoluble and soluble and silver metal	Firecracker maker, silver nitrate worker, silver polisher, silversmith	Yes	Yes	Yes	NA
						Localized discoloration in silversmiths only, none of whom had systemic disease		Slit-lamp examination	
Hill & Pillsbury (36)	Case series	40	Silver aluminate, silver chloride, silver fulminate, silver nitrate, and silver metal	Insoluble and soluble and silver metal	Photographic plate maker, silver miner, silver nitrate worker, silver polisher, silver smelter, silversmith	Yes	Yes	Yes	NA
								"Argyrosis of the eyes is described all the cases of generalized occupational argyria, and 6 cases of the local type [p 125]."	
Remler (37)	Case series	31	Silver bromide and silver nitrate	Insoluble and soluble	Photographic and X-ray film emulsion worker	NA	NA	Yes	No
								"... the predominant features of occupational argyrosis are conjunctival argyrosis and its negative cosmetic effect [p 705 (author's translation)]"	
Perrone et al (5)	Case report	4	Silver metal	Silver metal	Silver polisher	No	Yes	Yes	No
								Biomicroscopy	
Rosenman et al (1) and Moss et al (2)	Clinical study	30	Silver nitrate and silver oxide	Insoluble and soluble	Silver nitrate and silver oxide worker, clerk	NA	Yes	Yes	No
						Six employees (20 %) not confirmed by skin biopsy		Conjunctival (67 %) and corneal (50 %) deposition by slit lamp examination	
Bleehen et al (10)	Case report	5	? silver oxide and silver metal	? insoluble and silver metal	Silver smelter	NA	Yes	NA	NA
						Light and electron microscopy, and X-ray microanalysis			
Rosenman et al (3)	Clinical study	27	Silver nitrate, silver oxide, silver chloride, silver cadmium oxide	Insoluble and soluble	Metallurgical production and maintenance worker	NA	NA	Yes	NA
								Ten (37 %) and six (22 %) employees, respectively, had conjunctival (> 2+) and corneal (4+) deposition	

^a Inhalation was the primary route of exposure. Other types of exposures were oral (hand-to-mouth contamination, ingestion via pipetting), ophthalmic (rubbing fingers in eyes), and local (instillation through broken skin).

oxide, chloride, etc). The median duration of silver exposure in both of these studies was slightly more than five years compared with about 18 years in the current investigation.

As noted, limited information is currently available concerning the risks of argyria or argyrosis from insoluble silver compounds. In contrast to a clinical study of predominately silver nitrate workers (1), our investigation of recovery employees exhibited no evidence of systemic argyria as assessed by clinical examination and skin biopsy with electron microscopy and dispersive X-ray analysis. In addition, on the basis of an assessment of standardized facial photographs, layman and physician panels were unable to perceive a difference in either the frequency or severity of facial discoloration for the silver workers versus that of referents. There was, however, some internal local dis-

coloration of the nasal septum, apparently unrelated to the duration of employment and blood silver level. No increased pigmentation of the oral mucosa or gums was observed.

The lower prevalence of conjunctival argyrosis in the present investigation (21 %) in comparison with the prevalence determined in the Rosenman et al studies (1, 3) (67 and 63 %) may have been due, in part, to differences in silver speciation. In contrast, the corneal argyrosis findings at a metallurgical refinery (3) were similar (22 %) to those reported in the current study (25 %). The proportion was higher (50 %) for the silver nitrate and silver oxide workers (1).

Despite its frequent clinical presentation, there is general agreement that argyrosis causes no impairment of visual function. Furthermore, an association with

ents

ralized argyria of occupational origin was at no time a common condition. It is almost exclusively in makers of silver nitrate. Owing to changing conditions in the industry it is now fast disappearing [p 441]."

included 24 cases in addition to the 16 reported by Harker & Hunter (35)

ion of exposure 2 to 30 years

nated exposure 22 to 310 $\mu\text{g}/\text{m}^3$ as metallic silver; restrictive pulmonary function in two workers although no spirometric measurements given; carbon monoxide transfer reduced in three employees tested; however, data uncorrected for smoking and age; renal and hepatic functions normal

posure (silver metal) 39 to 378 $\mu\text{g}/\text{m}^3$; median duration of employment approximately five years; creatinine clearance reduced in five subjects (16%), ten reported decreased night vision; electroretinographic studies conducted on seven were normal; 12 had measurable blood silver levels

biopsies of four referents normal; selenium, mercury, titanium, and iron in workplace environment

age of 8-h time-weighted average 40 to 350 $\mu\text{g}/\text{m}^3$; mean tenure 8.1 years, other potential exposures included cadmium, formaldehyde, nitric and hydrochloric acids, hydroquinone, methanol, and oxides of nitrogen; excluding four hypertensives and/or proteinurics, the mean urinary N-acetyl-n-glucosaminidase (NAG) value was significantly higher in the silver workers than the comparison group of 3500 carbide machine operators; elevated blood silver, urinary silver, and titanium levels were observed in 92, 96 and 19% of employees, respectively.

nyctalopia has not been demonstrated. One-third of the silver workers studied by Rosenman et al (1) reported decreased night vision in their medical history. However, after conducting a series of tests (electroretinography, color-vision screening, visually evoked potentials, etc) to confirm these subjective complaints, Moss et al (2) concluded that, "no electrophysiologic or psychophysiologic deficit could be documented [p 908]." In addition, the results of contrast sensitivity studies were negative for four individuals tested by the Mt Sinai ophthalmologists, while the present epidemiologic investigation, which evaluated a larger number of subjects, showed no significant difference between the recovery workers and referents.

Silver polishers and finishers exposed to metallic silver, as well as to abrasive pastes and rouges, have been the primary occupational groups represented in the few

case reports which have addressed respiratory pathology. In 1945, McLaughlin et al (39) described clinical and radiologic findings for four silver finishers who were chronically exposed (20–40 years) to iron oxide (from rouges), cotton, and silver dusts. Three of the employees had a history of cough accompanied by red-black sputum; no other pulmonary signs or symptoms were reported. Radiographic examination revealed the presence of reticulation in the lung fields, "resembling that found in welders, in haematite miners, and in other workers who inhale iron and iron oxide dust [p 340]." With the exception of one case of emphysema, no physical disability was observed. Silver was not implicated.

Barrie & Harding (40) in 1947 described postmortem examinations of four British silver finishers [including one of the McLaughlin et al (39) cases] who were also exposed to iron oxide and silver dusts. Microscopic and histochemical analyses showed silver impregnation of the alveolar walls and small pulmonary vessels. Three of the four had no history of respiratory disability; one complained of a chronic cough. While all the cases were emphysematous, the authors concluded that these findings were not unusual since, "most Sheffield workmen have well-marked emphysema at the age of 60 [p 228]." No information was available concerning smoking history.

In a 1977 case report, Perrone et al (5) described pulmonary function and chest radiographic results for four Italian silver polishers with long-term (25–30 years) exposure to silver particles and dusts from abrasive pastes (composition unknown) and fabric and vegetable fibers. Increased bronchovascular markings, reduced lung capacity (restrictive syndrome), and diminished carbon monoxide transfer were noted in two employees, both of whom were smokers (approximately 20 cigarettes per day). It is difficult to interpret the extent to which silver contributed to these findings since the work environment included multiple agents, some of which may have been fibrogenic. In addition, the carbon monoxide transfer testing methodology and comparative values were unreferenced.

There was no evidence of restrictive pulmonary disease in the Rosenman et al (1) study; obstructive changes were essentially limited to smokers and ex-smokers. In addition roentgenographic examination did not show increased bronchovascular markings. However, it should be noted that, while these employees were exposed to relatively high levels of silver nitrate and silver oxide, they were not subjected to the fibers, abrasives, and dusts characteristic of silver polishing.

The negative pulmonary results in the current investigation are consistent with those reported by the Mt Sinai physicians. Cigarette smoking was apparently the most important risk factor associated with both respiratory symptoms and decreased pulmonary function. In addition, the chest radiographs were essentially negative in both the study and comparison groups.

Histochemical analyses of deceased persons with argyria have demonstrated high concentrations of silver in the kidney (41). However, the toxicologic significance of this finding is unclear. Zech et al (4) described a case of nephrotic syndrome with increased blood urea nitrogen and creatinine in a 73-year-old man who had used silver-containing mouthwash for 10 years; his estimated cumulative dose of metallic silver was 88 g. Renal biopsy revealed an endarteritis, as well as silver deposits in the basal glomerular membranes. Since no information was available concerning a history of hypertension, diabetes, or chronic medication usage and since a therapeutic response occurred following the administration of an antiinflammatory drug, the etiology of this unusual case of nephrosis in a person with argyria is uncertain.

Abnormal creatinine clearance values were observed in five of the 30 study subjects examined by the Mt Sinai researchers (1). Hypertension, reported for three of these individuals, could have influenced renal function. The authors indicated that "no other (than blood pressure) etiologic factors were elicited" and that "additional studies will have to be done to further investigate possible kidney damage [p 434]." Compared with the levels of their unexposed referents, significantly lower creatinine clearance values (unrelated to either blood or urine silver concentrations) were observed in the New Jersey metal refinery workers studied by the same principal investigator (3). In addition, the N-acetyl- β -glucosaminidase (NAG) levels were significantly elevated in the silver-exposed workers (four subjects having extreme values) versus those of the referents. In interpreting this finding, the authors stated that "... it is not possible to determine if the observed NAG rises are due to silver deposition or other renal toxins such as cadmium [p 271]." Furthermore, the researchers did not assess the potential confounding effect of aspirin on the NAG levels (42). (This medication may have been used since more than one-half of the study group reported upper and/or lower respiratory symptoms.) The current study, in contrast, found no dose response or significant differences in renal function between the silver recovery workers and their referents, both groups exhibiting similar creatinine clearance, blood urea nitrogen, and urinary protein findings. It should be noted, however, that sensitive measurements for identifying renal dysfunction such as the urinary excretion of β -2-microglobulin and tubular enzymes were generally unavailable at the time the study was conducted.

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Appendix

Study methods

Facial photograph study

Full-face color photographs (8 × 10 inches, ie, approximately 20 × 25 cm) of each subject were made under controlled conditions (lighting, camera setting, subject position, time of year). The film (Kodak Vericolor II, type S) was selected from the same emulsion block; the photographic paper was similarly chosen. Developing and printing operations were also standardized. In order to prevent color reflection from clothing and to avoid identification of an employee's job based on his workclothes, a neutral colored cloth was draped over the neck and shoulder area. As an additional constraint during the photographic review, each portrait was covered with a paper mask which allowed only the subject's face to be visualized. Since photographs of two recovery employees and one reference subject were not taken, the study population for this experiment was reduced to 24 worker-referent pairs.

The photographs were reviewed by 23 judges assigned to the following three panels: panel 1: laymen (clerks and technicians from our laboratory, N = 12); panel 2: research physicians (administrators and toxicologists from the same laboratory, N = 5), and panel 3: clinical physicians (occupational physicians from two plant medical departments, N = 6).

After the judges read a brief instructional statement, they were given a card describing the categories to be used for ranking the individuals according to the extent of their cosmetic impairment. Each pair of portraits was then examined in sequence. The reviewers were first asked to select the person with facial discoloration and then to score that individual on a scale of 1 to 5; the second photograph was scored 0. The study subjects were reviewed in pairs rather than individually because of the strong association between age and the presence of acne, nevi, and other facial blemishes.

Figure 1. Schematic diagram of the contrast sensitivity experiment.

Electron microscopy study

Fixed blocks initially immersed in 5 % glutaraldehyde and later in Dalton's chrome-osmium solution were dehydrated in a graded series of mixtures of ethanol and propylene oxide and embedded in Epon 812®. Thick sections were stained with toluidine blue and examined by brightfield and darkfield microscopy. Thin sections were collected on 200-mesh copper grids. Sections stained with uranyl acetate and lead citrate and unstained sections were examined with a Philips 201 electron microscope. Selected unstained sections collected on carbon-coated nonmetallic grids were evaluated with a JEOL 100CX electron microscope equipped with a Kevex 7000 energy-dispersive X-ray microanalysis unit.

Contrast sensitivity study

Contrast sensitivity measurements were obtained by the technique known as Wetherill tracking (1). The data were collected by means of a computer-controlled apparatus designed and constructed by a psychophysicist (RTK) in this laboratory (2). A schematic of the test device, which was based on a model developed by Carlson & Heyman (3), is shown in figure 1.

A target of light and dark vertical bars in the form of a sinusoidal grating pattern was presented to the subject by rear projection onto a screen from a 35-mm slide. Contrast was altered by the changing of the relative positions of a translucent diffusion screen between the subject and the projected image. Depending upon the subject's response, the diffusing screen was moved a fixed number of steps either closer to or away from the stimulus, the visual contrast pattern thus being altered. In addition to recording total responses, the computer calculated the mean number (and variance)

of "counts" (steps separating the stimulus from the diffusing medium) for each threshold level. A large value was associated with a low contrast pattern and high sensitivity.

Prior to the experiment, refractive errors were corrected optimally for each subject using corrective lenses, where appropriate. Following a brief introduction, which included detailed operational instructions, the subject was shown an easily recognizable test pattern. The session was initiated by a switch being pressed which caused two slides, randomly selected as either a blank or a sinusoidal grating, to be displayed sequentially at 0.5-s intervals. After either the first or second was chosen as the grating pattern (by the keying of the appropriate response), the diffusion screen was positioned to the next stimulus level under program control. This process was repeated until the final threshold level was reached on the basis of a predetermined criterion response probability. For this experiment, in which this value was 0.71, two consecutive correct responses were required in order to lower the stimulus level (increase the distance between screens), whereas an incorrect response raised it.

Measurements were made for four spatial frequencies (5.9, 7.5, 8.3, and 14.5 cycles per degree of arc subtended by the ocular viewing angle) under both normal illumination and with a bright point light source (incandescent lamp) located approximately 30° in the peripheral visual field. The glare condition could be expected to enhance the effect of light scattering on contrast sensitivity. The eight viewing conditions (four spatial frequencies $\times$ two illumination types) were presented to the subject in a partially randomized manner (not more than two of the same kinds of lighting were permitted in succession). Each subject completed the session in approximately 50 min.

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