

# Endocrine and Reproductive Dysfunction in Men Associated with Occupational Inorganic Lead Intoxication

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**ABSTRACT.** In an attempt to define a postulated effect of lead on male endocrine function, seven men with symptomatic occupational lead intoxication (maximum whole blood lead levels 66–139  $\mu\text{g}/\text{dl}$ ) underwent in-patient endocrine evaluation at the time of diagnosis. Defects in thyroid function, probably of central origin, were present in three patients. Six patients had subnormal glucocorticoid production measured by 24-hr urinary 17-hydroxycorticosteroids and plasma cortisol responses to vasopressin- and/or insulin-induced hypoglycemia. Although serum testosterone concentration was normal in six patients, five had defects in spermatogenesis, including two with oligospermia and two with azospermia. Repeat examinations after chelation therapy showed only partial improvement. It is concluded that heavy occupational exposure to lead, sufficient to cause clinical poisoning, may be associated with diffuse disturbances of endocrine and reproductive functions in men which are not rapidly reversible with standard treatment. Since men without overt poisoning have not been studied, these results cannot yet be included as sequelae of low-dose exposures.

IT HAS BEEN RECOGNIZED for over a century that women occupationally exposed to lead were frequently infertile.<sup>1</sup> Many historic accounts suggested that spouses of exposed men also experienced reproductive dysfunction.<sup>2</sup> These reports predate modern industrial hygiene, methods of quantifying biological exposure, and the technology to evaluate the pathophysiologic defects responsible.

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In the past 2 decades, effects of lead on male endocrine and germinal tissue have been investigated. Lancranjan, studying industrial workers, reported dose-related oligospermia and athenospermia.<sup>3</sup> Braunstein et al.<sup>4</sup> have reported defects in both spermatogenesis and central regulation of testicular androgens in men chronically exposed to lead who were referred for observation because of sexual and reproductive dysfunction. Studying patients with lead poisoning from ingestion of illicit whiskey, Sandstead found depressed production of urinary cortisol metabolites both before and after metapyrone challenge.<sup>5</sup> Recently, Robins et al.<sup>6</sup>

described a high prevalence of central hypothyroidism in workers with lead poisoning. Additionally, these investigators<sup>6</sup> demonstrated a dose-responsive depression of thyroxine and estimated free thyroxine in a cross-sectional study of men at a brass foundry. All of these studies have focused on heavily exposed subjects, often with other manifestations of lead poisoning.

During the past 18 months, we have attempted to verify these findings and better define the pathophysiology of endocrine and reproductive impairment in lead-poisoned men. In the present report we describe the spectrum of endocrine function at presentation in seven patients referred to an occupational medicine clinic because of lead intoxication. Our results extend the available database on hormonal and germinal dysfunction in men with lead poisoning and suggest hypotheses about the effects of lead on the endocrine system. Additionally, we report preliminary data on the response of these lesions to chelation therapy for lead intoxication.

## MATERIALS AND METHODS

Thirty-one cases of adult inorganic lead intoxication have been diagnosed at the Yale Occupational Medicine Clinic among some 55 cases referred since 1979. Seven of these agreed to participate in an in-patient evaluation of endocrine and reproductive function and form the basis of the present report. Among the 22 who did not participate, 12 had already been treated prior to institution of the protocol. Nine refused the protocol, primarily because of work commitments. One was too old (i.e., > 50 yr). Compared to those who refused, study patients had more complaints of sexual dysfunction (3/7 vs 1/9) and had higher blood lead levels ( $73.0 \pm 19 \mu\text{g}/\text{dl}$  vs.  $51.7 \pm 14 \mu\text{g}/\text{dl}$ ) than those who did not participate. Details of the population from which study patients were drawn have been reported separately.<sup>7</sup>

The following studies have been performed on most or all of the patients prior and subsequent to treatment:

1. Whole blood lead level by flameless atomic absorption spectrophotometry. (The laboratory participates in the CDC quarterly lead testing program and has been approved throughout the conduct of the study.)
2. Free erythrocyte protoporphyrin by method of Piomelli.<sup>8</sup>
3. Zinc protoporphyrin using the protoporphyrin fluorescence standard kit supplied by Porphyrin Products, Logan, Utah.
4. Complete blood count by coulter counter.
5. Whole blood smear stained with Wright solutions.
6. Urinalysis.
7. Serum creatinine and urea nitrogen.
8. Twenty-four hour urine for creatinine.
9. Serum uric acid.
10. Serum aspartate aminotransferase (SGOT), alkaline phosphatase, direct and indirect bilirubin.
11. Thyroid function tests by the competitive binding protein method of Seligson.<sup>9,10</sup>
12. Total triiodothyronine ( $T_3$ ) by double radioimmuno assay using a commercial kit purchased from Nichols Laboratory.
13. Semen analysis using a freshly ejaculated specimen obtained after at least 3 days abstinence.
14. Total serum testosterone using a commercial kit purchased from Serone Laboratories and free serum testosterone using a modification of the method of Moll and Rosenfield.<sup>11</sup>
15. Plasma cortisol by the fluorometric method of Mattingly.<sup>12</sup>
16. Thyrotropin (TSH) by radioimmune assay with a modification of the method of Odell.<sup>13</sup>
17. Serum leutinizing hormone (LH) and follicle stimulating hormone (FSH) by double radioimmune assay using a commercial kit purchased from Serono Laboratories.
18. Prolactin by a double antibody method with antibody and standard purchased from Cal Biochem (California), and isotopically labeled prolactin from Serono Laboratories.
19. Thyrotropin releasing hormone (TRH) stimulation test measuring prolactin and TSH 10, 20, 30, 40, 50, 60, 90, and 120 min after administration of 500  $\mu\text{g}$  TRH by rapid intravenous (i.v.) bolus.
20. Insulin tolerance test measuring plasma glucose, cortisol, and growth hormone 15, 30, 45, 60, 90, and 120 min after i.v. administration of 0.15 units regular insulin/kg body weight or a higher amount sufficient to lower plasma glucose below 35 mg/dl.
21. Water deprivation test measuring serum and urine osmolality and cortisol before and after administration of intramuscular vasopressin by the protocol of Miller and Moses.<sup>14</sup>
22. Seventeen hydroxy steroids measured in a 24-hr urine collection by the method of Silber.<sup>15</sup>
23. Urinary free cortisol by radioimmunoassay.
24. Seventeen ketosteroids measured in 24-hr urine collection by the method of Chaney.<sup>16</sup>
25. Formal neuropsychological evaluation of: intelligence utilizing subtests of Wechsler Adult Intelligence Scale (WAIS); rapid sustained fine motor control utilizing times finger tap; visual-tactile dexterity employing the Lafayette pegboard; grip strength using a dynamometer; memory testing using the paired associates subtest of the Wechsler Memory Scale; and higher order visual spatial abilities measured by the Ravens progressive matrices.
26. Cone down radiographs of the sella turcica and assessment of visual fields.

In addition to these tests, case 7 had measurement of LH and FSH at 0, 1/2, 1 1/2, 2, 2 1/2, 3, 3 1/2, 4, and 24 hr after i.v. injection of 0.1 mg of LH releasing hormone. Case 7 also had measurement of plasma cortisol at 0, 15, 30, 45, and 60 min after intramuscular injection of 250  $\mu\text{g}$  of synthetic ACTH (cortrosyn). Two patients also underwent surgical testicular biopsy for evaluation of azoospermia.

All studies were performed during a 3-day in-hospital stay on the Clinical Research Center of Yale-New Haven Hospital after obtaining written consent from the subjects. The protocol and consent forms had been approved by the Yale School of Medicine Human Investigations Committee. Blood and urine tests were performed in the clinical laboratories of the Hospital

**Table 1.—Demographic and Clinical Data on Study Patients**

Case	Age (yr)	Race	Occupation	Duration of Exposure	Symptoms	Blood Lead (µg/dl)	Maximum Blood Lead (µg/dl)	Clinical Syndrome	Organ System Involvement	Other Medical History
1	42	Black	Shake out man (brass foundry)	11 yr	impotence, infertility	66	66	chronic	renal, central nervous system	lichen simplex et chronicus
2	43	Black	Furnaceman (brass foundry)	15 yr	back pain	66	110	chronic	renal, central nervous system	adult onset diabetes mellitus; heavy alcohol use
3	22	White	Storage battery maker	6 mo	abdominal pain, fatigue, impotence	83	83	acute	colic, hemolytic anemia, renal	—
4	36	Black	Chemical operator	2 mo	abdominal pain, headache, paresthesias	98	98	acute	colic, central and peripheral nervous system, hepatic	—
5	30	White	Painter	4 yr	abdominal pain, fatigue, irritability, arthralgia, depression, decreased libido	70	139	acute & chronic	central nervous system, colic hemolytic anemia, hepatic	intermittent heavy alcohol use
6	37	White	Painter (avocational)	5 wk	abdominal pain, fatigue, irritability	90	97	acute	colic, hemolytic anemia	—
7	32	Black	Storage battery maker	7 yr	arthralgia, irritability, abdominal pain	39	80	chronic	central nervous system, renal, hepatic	—

**Table 2.—Results of Tests of Thyroid Function in Study Patients**

Case	Thyroxine (T <sub>4</sub> ) (µg/dl)	Thyroid Binding Globulin (µg/dl)	Estimated Free Thyroxine (ng/dl)	Total Triiodothyronine (T <sub>3</sub> ) (ng/dl)	Thyroid Stimulating Hormone (TSH) (uU/ml)	TSH response to Thyrotropin Releasing Hormone (TRH Stimulation) (uU/ml)
Normal	4.6–9.2	16.8–25.7	1.0–2.1	80–200	< 7	Rise from Baseline ≥ 5*
1	4.5	24.5	0.8	98	4	normal
2	4.2	22.8	0.6	93	4	normal
3	7.8	21.5	1.7	155	2	normal
4	8.9	29.0	1.5	180	3	normal
5	7.8	23.8	1.5	130	1	normal
6	4.7	20.8	1.1	100	1	normal
7	6.9	29.2	1.1	120	5	flat baseline 6 (peak 7)

\* See reference 26.

except for the urinary cortisol which was performed by Nichols Laboratory. Comparison has been made to the laboratory reference range. For the challenge studies, normative data has been drawn from standard reference texts.<sup>25,26</sup>

**RESULTS**

**Demographic and clinical background.** The study patients were men aged 22 to 43 yr (mean 35 yr) all

who lived and worked in Connecticut. Exposures to lead occurred at five workplaces in six patients and avocationally in one. Durations of exposure ranged from 5 wk to 15 yr with three cases less than 6 months. Four patients had typical symptoms of acute intoxication with lead colic; three had clinical diagnoses of chronic poisoning dominated by diffuse central nervous system dysfunction and renal involvement. Clinical summaries, demographic and exposure data are sum-

**Table 3.—Results of Tests of Adrenocortical Function in Study Patients**

Case	Weight (kg)	Urinary Creatinine (mg/kg • 24 hr)	24-hr Urinary 17 Hydroxy-Steroids (mg/24 hr)	24-hr Urinary 17 Ketosteroids (mg/24 hr)	24-hr Urinary Free Cortisol ( $\mu$ g/24 hr)	Insulin Tolerance Test (Cortisol) ( $\mu$ g/dl)	Water Deprivation Test (Cortisol) ( $\mu$ g/dl)	Cortrosyn Stimulation (Cortisol) ( $\mu$ g/dl)
Normal Values		$\geq 15.0$	$\geq 3.0$	$\geq 8.0$	20–100	Rise in Baseline > 10; Peak > 20*	Double Baseline Peak > 25*	Double Baseline Peak > 20*
1	99	10.6†	1.6	2.9	20	normal	flat (baseline 11) (peak 11)	not done
2	70	18.3	2.6	10.9	49	normal	flat (baseline 12) (peak 17)	not done
3	80	22.0	1.7	8.6	< 20	borderline (baseline 13) (peak 22)	borderline (baseline 12) (peak 21)	not done
4	93	20.5	5.4	15.0	54	inadequate test	flat (baseline 23) (peak 25)	not done
5	84	18.6	3.6	11.1	not done	normal	flat (baseline 16) (peak 16)	not done
6	77	25.3†	4.6	19.2	not done	normal	not done	not done
7	62	23.5†	2.0	11.2	not done	flat (baseline 15) (peak 20)	flat (baseline 14) (peak 15)	normal

\* See references 25 and 26.  
 † Repeated two times.

marized in Table 1. Case histories and results of clinical evaluations are presented below.

**Case 1.** This 42-yr-old foundryman was referred by his local union representative because of complaints of impotence of several years duration. He had been without medical problems other than neurodermatitis. Specifically, although he had no children, he reported normal sexual function prior to onset of presenting symptoms. He denied exposure to alcohol, drugs, or other gonadal toxins.

Physical examination revealed chronic diffuse dermatitis and small testes. Hair pattern and body habitus were normal. Gynecomastia was absent. Laboratory studies revealed lead level of 55  $\mu$ g/dl and free erythrocyte protoporphyrin of 533 (normal: < 40 units). Blood count, peripheral smear, urinalysis, and serum liver function tests were normal. Uric acid was elevated at 6.8 mg/dl. Creatinine clearance was 60 cc/min. Neuropsychological tests revealed deficits of fine motor, visual motor, and non-verbal adaptive abilities.

**Case 2.** This individual was 43 yr old and was referred from the same foundry as Case 1 because of persistent back pain. He was in good health but had been told of glucose intolerance, treated with diet. He drank 1/2 pint whiskey daily. He had two teenage children and denied reproductive or sexual problems. Work records revealed he had had a blood lead level of 110  $\mu$ g/dl 1 yr prior to referral.

Physical examination was unrevealing. Laboratory tests demonstrated blood lead of 66  $\mu$ g/dl. Free

erythrocyte protoporphyrin level was 345 units. Routine blood work was normal except for a slight elevation of SGOT. Creatinine clearance was 72 cc/min. Uric acid was normal. Neuropsychological tests revealed deficits of short-term memory, motor control, and non-verbal intelligence.

**Case 3.** This young newlywed had worked in a family-run storage battery-making plant for 6 months before developing colic. He was referred 6 wk after an appendectomy had failed to relieve his pain. He noted also irritability and some recent sexual dysfunction. There was no history of exposure to gonadal toxins or prior medical illness.

Physical examination was normal. Lead level was 83  $\mu$ g/dl with zinc protoporphyrin level of 285 (normal: < 28 units). Laboratory findings included hemoglobin of 10 gm/dl with marked reticulocytosis and basophilic stippling. Uric acid was 10.4 mg/dl. Liver function, neuropsychologic performance, and creatinine clearance were normal.

**Case 4.** This 36-yr-old chemical operator presented to the emergency room with headaches, abdominal pain, and paresthesias in his left arm. He had been in excellent health until several weeks earlier. Notably, he had been transferred 2 months before from an office job to work as floor supervisor in the manufacture of lead salts. Reproductive and sexual history were normal. He is a social consumer of alcohol.

Physical examination was remarkable for impaired sensation in a C<sub>5-6</sub> distribution. Laboratory studies were note-

worthy for elevated uric acid (9.2 mg/dl) and blood lead (98 µg/dl). Zinc protoporphyrin was 132 units. SGOT was elevated at 64, but complete blood count, 24-hr urine for creatinine clearance, alkaline phosphate, and bilirubin were normal. Neuropsychological tests showed mild impairment of motor and cognitive function.

**Case 5.** This 30-yr-old unmarried house renovator and painter had been complaining of insomnia, arthralgia, and depression for almost a year. The development of colic, anosmia, and headache coincident with paint stripping from a Victorian house prompted determination of blood lead which was elevated at 139 µg/dl. He was intermittently a heavy alcohol drinker but had not prior medical history.

On referral 2 months later, all symptoms persisted. Physical examination was unremarkable except for impaired olfaction. Laboratory studies revealed a lead

level of 70 µg/dl and a zinc protoporphyrin level 222. Hemoglobin was 12.3 gm/dl and both reticulocytosis and basophilic stippling were present. SGOT was elevated slightly, but all other liver functions were normal. Urinalysis, uric acid, and glomerular filtration were normal. Neuropsychological testing could not be obtained prior to treatment but liaison psychiatry referral confirmed the clinical impression of organic depression.

**Case 6.** A 37-yr-old engineer was exposed to lead while renovating his home; he spent 5 wk burning and sand blasting the outdoor paint. One week later he developed colic and was admitted to an outside hospital. Observation of a lead line prompted referral to Yale. Past history was unremarkable. He had three healthy children and had had a vasectomy several years before. He is a nondrinker.

Physical exam revealed a pale man with a striking

**Table 4.—Results of Studies of Gonadal Function in Study Patients**

Case	Sperm Count (million/ml)	Semen Volume (ml)	% Motile Sperm	Serum Morphology	Total Testosterone (ng/ml†)	Free Testosterone (ng/ml)	LH (mIU/ml†)	FSH (mIU/ml†)	Prolactin (ng/ml†)	Other Studies
Normal Values	> 20		> 50		2.0–8.0	1.0–4.0	2–20	2–10	≤ 20	
1	0*	1.0	—	—	3.26	1.14	56	30	20	cytogenics—46, X,Y; Biopsy—testicular atrophy with absent spermatogenesis, basement membrane thickening, peritubular hyalinization and focal Leydig cell hyperplasia
2	18	2.0	40	61% dead 10% dying 29% live 95% normal 55% abnl	4.56	2.12	8	3	6	
3	12	2.0	11	62% dead 9% dying 9% live 36% normal 64% abnl	6.26	3.88	5	3	18	
4	49	3.0	59	33% dead 15% dying 52% live 80% normal 20% abnl	3.66	2.09	2	1	8	
5	48	3.5	25	73% dead 5% dying 22% live 80% normal 20% abnl	4.05	1.38	3	2	26	
6	vasectomy	—	—	—	3.89	1.79	16	4	14	
7	0*	1.5	—	—	6.23	2.62	14	21	9	normal LH & FSH rise to LHRH challenge; Biopsy—focally depressed spermatogenesis. Multiple seminiferous tubules with sertoli cells only. Focal Leydig cell hyperplasia; cytogenics—46 X,Y

\* Based on evaluation of two separate specimens.

† Average of at least 2 separate determinations.

**Table 5.—Endocrine Function After Chelation Therapy**

Case	Months After Initial Diagnosis	Post-Treatment PbB ( $\mu\text{g}/\text{dl}$ )	Thyroid Function	Adrenal Cortical Function	Gonadal Function
1	23	20	$T_4$ and estimated free thyroxine return to lowest limits of normal (5.4 $\mu\text{g}/\text{dl}$ and 1.0 ng/dl, respectively).	17-hydroxysteroids return to normal (4.7 mg/24 $^{\circ}$ ). Rest no change.	Azoospermic, no change. Testosterone, LH, FSH, PRL no change.
3	5	34	No change.	17-hydroxysteroids return to normal (5.1 mg/24 $^{\circ}$ ). Free cortisol remains < 20 $\mu\text{g}/24^{\circ}$ . 17-keto steroids no change. Challenge tests improve to adequate.	Sperm count rise to 39 million with 29% motile, 80% normal morphology. Testosterone, LH, FSH, PRL no change.
4	8	56*	No change.	No change.	Sperm count drop to 15 million with 20% motile, 74% normal morphology. Testosterone, LH, FSH, PRL no change.
5	4	23	No change.	No change.	Sperm count rise to 64 million with 62% motile, 77% normal morphology. Testosterone, LH, FSH, PRL no change.
7	3	27	No change.	17-hydroxysteroids return to low normal (3.4 mg/24 $^{\circ}$ ). Rest no change.	Azoospermic, no change. Testosterone, LH, FSH, PRL no change.

\* Re-exposed to lead subsequent to treatment.

gingival lead line. No other symptoms were noted. Lead level was 90  $\mu\text{g}/\text{dl}$ , zinc protoporphyrin 135 units. Hemoglobin was 11 gm/dl with high reticulocyte count without basophilic stippling. Tests of liver and renal function were within normal limits, as was measured neuropsychological performance.

**Case 7.** Case 7 was referred to this clinic 16 months after his lead battery plant had closed; he had recently been refused work because of a high lead level. He had developed diffuse arthralgias, intermittent abdominal pains, and irritability during his 7 yr making batteries. Lead level had ranged between 60 and 80  $\mu\text{g}/\text{dl}$  based on plant records. Complaints had diminished since leaving work, but persisted mildly. He had three healthy children, the youngest 4 yr old, and the patient used contraception regularly. He is a moderate drinker.

Physical exam was abnormal only for slightly small testes of normal texture. Secondary sexual characteristics were normal. Blood lead was 39  $\mu\text{g}/\text{dl}$ . Zinc protoporphyrin was normal at 22 units. Blood uric acid level was low. Creatinine clearance was 82 cc/min. Neuropsychological performance was diffusely impaired.

**Thyroid function.** Results of the several tests of the integrity of the thyroid-pituitary hypothalamic axis are summarized in Table 2. Cases 1 and 2 had subnormal serum values of thyroxine and estimated free thyroxine with normal levels of TSH and normal TSH response to infused TRH. Case 7 had normal serum thyroxine but elevated binding globulin. Although estimated free thyroxine remained within the normal range, the response to TRH was nil (baseline 6, peak 7). Triiodothyronine ( $T_3$ ) levels were normal in each of these subjects. All other patients were normal for every parameter measured.

**Adrenocortical function.** Measurement of glucocor-

ticoid production by 24-hr urine 17-hydroxy-corticosteroid, and free cortisol levels and plasma cortisol response to insulin-induced hypoglycemia and vasopressin were subnormal in most patients. Two patients (Cases 3 and 7) were abnormal in each study. Case 7 showed a normal response to Cortrosyn stimulation on further testing. Two others (Cases 1 and 2) had normal responses to hypoglycemia despite low levels of urinary glucocorticoid metabolites and subnormal response to vasopressin. Patients 4 and 5 each failed to respond adequately to vasopressin although baseline cortisol values at 23  $\mu\text{g}/\text{dl}$  and 16  $\mu\text{g}/\text{dl}$ , respectively, were higher than in other patients. Notably, all subjects were able to concentrate their urine to greater than 850 mmole/L in response to dehydration prior to vasopressin challenge. Case 6 had a normal response to insulin hypoglycemia as well as normal urinary 17-hydroxy-corticosteroids; vasopressin response was not tested. Adrenal androgen production, measured by 24-hr urinary 17-ketosteroids, was within the predicted range on all patients but Case 2, who was also the only patient with depressed testicular androgen production (see below). These data are summarized in Table 3.

**Testicular function.** Results of tests of gonadal function are summarized in Table 4. Serum testosterone and free testosterone levels, reported as an average of two separate determinations, were normal in all men except Case 1, who had a borderline low level of free testosterone. Serum leutinizing hormone was repeatedly elevated in that case and normal in others.

Germinal function, however, was initially abnormal in most patients. Of six non-vasectomized patients, four had fewer than 20 million sperm per ml after abstinence; two (Cases 1 and 7) were azoospermic. Decreased

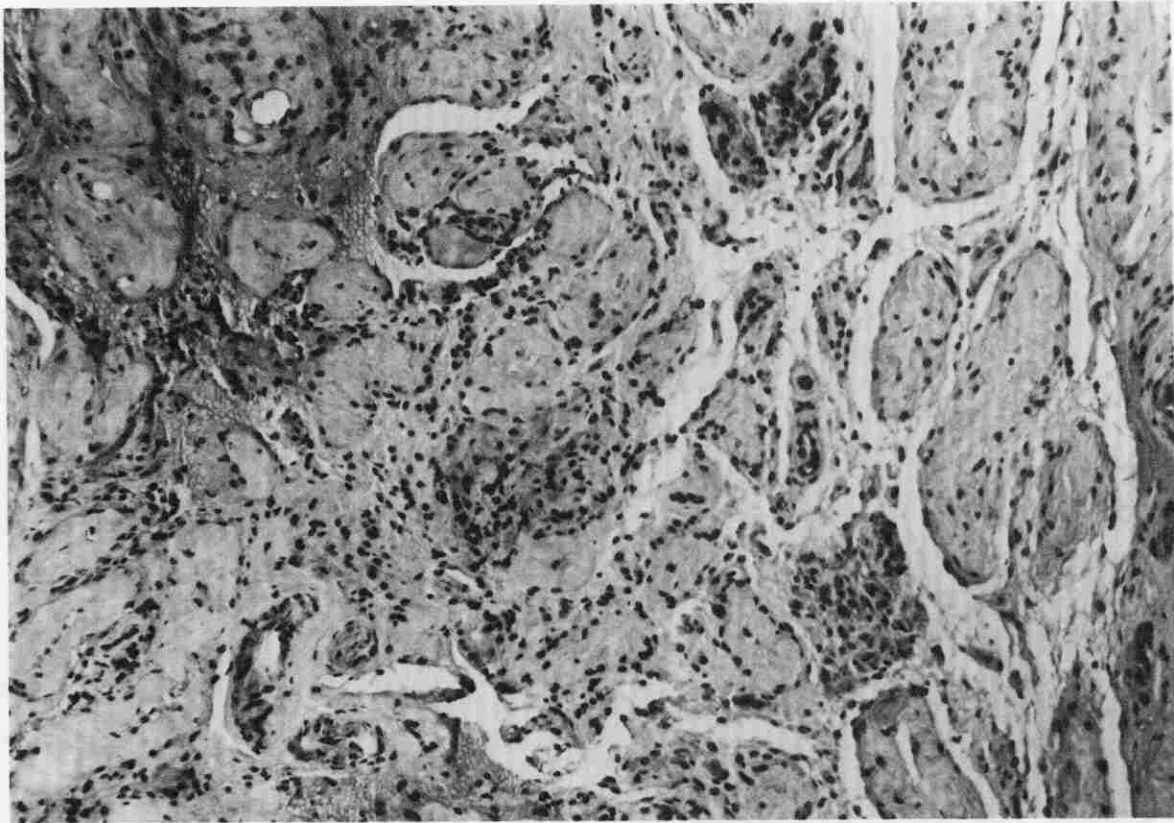
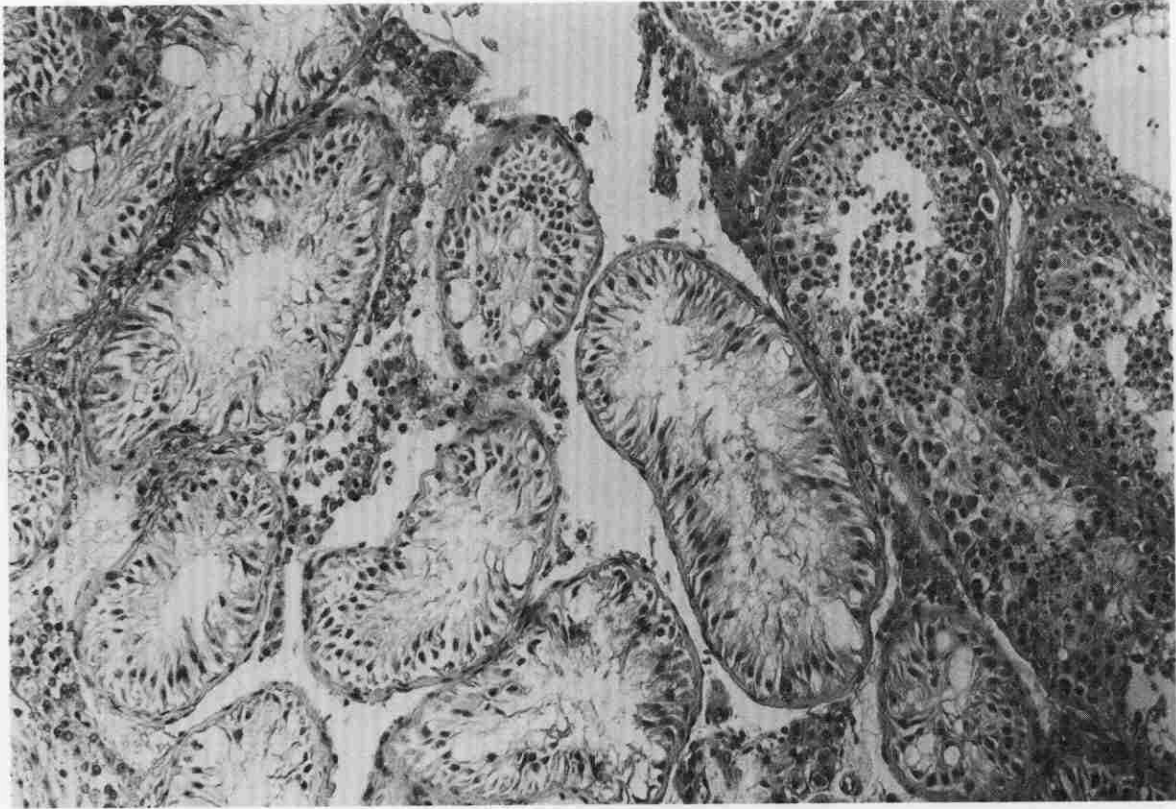


Fig. 1 (A and B). Testicular biopsy of patient 7. 1A demonstrates a spectrum of changes including aspermic tubules with sertoli cell hyperplasia and interstitial cell hyperplasia on *left*; adjacent tubules (*right*) contained formed sperm, but there is a moderately severe maturation disturbance. 1B, another portion of the same biopsy, showing more severe changes of tubular atrophy and sclerosis. (Magnification 100X, A and B)

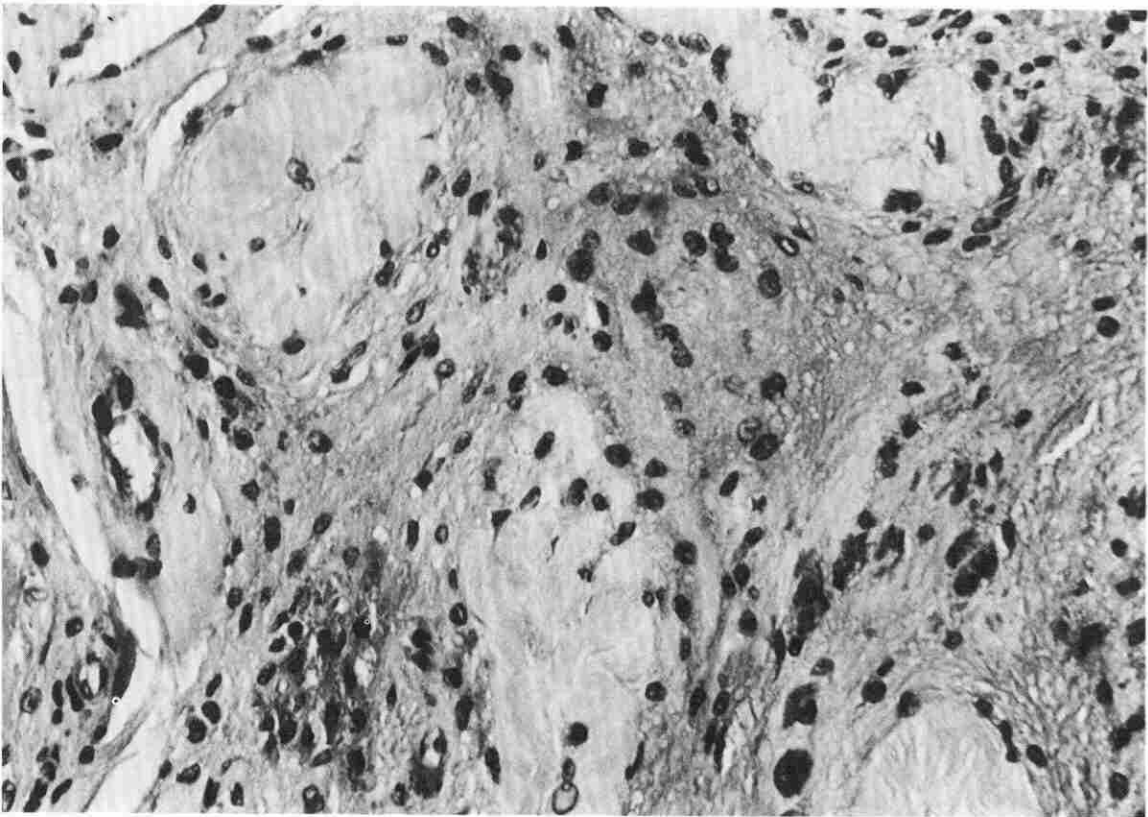
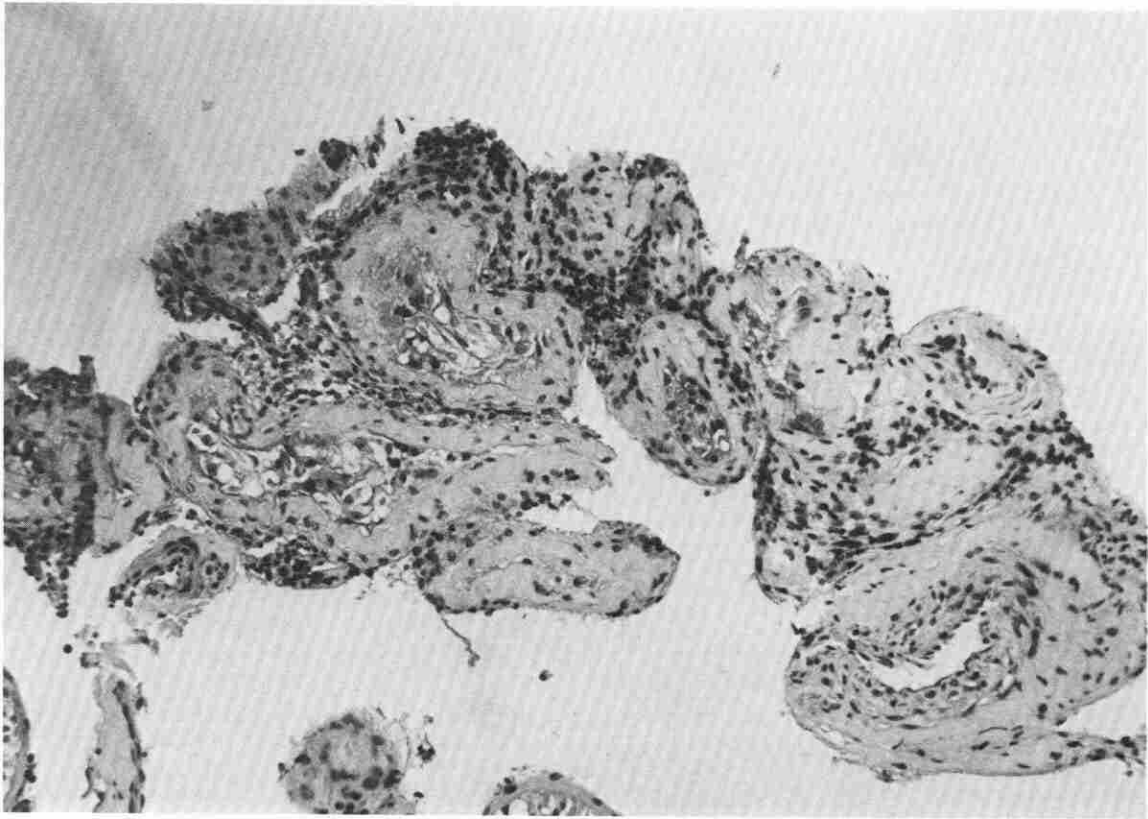


Fig. 2 (A and B). Testicular biopsy of patient 1. In 2A, severe atrophic changes are present in all fields of the biopsy. Tubules are hyalinized (center) and adjacent testis is scarred due to a combination of interstitial and tubular sclerosis. Prominent groups of nucleated cells are hyperplastic interstitial cells. At higher power (2B), acellular remnants of tubules are seen. Note the marked interstitial cell hyperplasia. (Magnification 100X, 2A; 250X, 2B)

sperm motility was evident in all but Case 4. Follicle stimulating hormone was repeatedly elevated in serum in both azoospermic men and normal in the others.

Azoospermic patients were studied further. Lymphocyte cytogenetics showed normal 46 XY compliments in each. Testicular biopsies, shown in Figures 1 and 2, revealed markedly depressed spermatogenesis, Leydig (interstitial) cell hyperplasia, and tubular and interstitial fibrosis. Patient 7 was challenged with gonadotropin releasing hormone (LHRH) and had a normal response.

Finally, slight hyperprolactinemia was present in Case 5. Borderline values were measured in Cases 1 and 3 while the remainder were normal. All prolactin responses to TRH stimulation were normal.

**Follow-up examinations.** All patients were treated in the hospital with 3 gm CaEDTA intravenously daily for 2-3 days and discharged on oral penicillamine (1 gm daily) until each patient's whole blood lead level was below 30  $\mu\text{g}/\text{dl}$  (2-6 months). Hormonal replacement was limited to depot testosterone (300 mg) monthly in Case 1. Five patients consented to have follow-up examinations after treatment. Unfortunately, patient 4 was significantly re-exposed to lead at work prior to retesting.

The results of the follow-up examination are summarized in Table 5. Modest increments in 24-hr excretion of hydrocorticosteroids were consistent and could not be explained by slight changes in renal function or collections. Thyroid function improved slightly in Case 1. Semen analysis showed a tendency toward improvement in two patients with acute poisoning (Cases 3 and 5) and deterioration in Case 4, who had been re-exposed to lead. Neither androgen production nor pituitary hormonal levels, baseline or in response to provocative challenge, showed any change after treatment.

## DISCUSSION

Several investigations reported during the past decade have suggested that heavy lead exposure causes depressed endocrine function and spermatogenesis.<sup>3-6</sup> The results of our studies, showing diffuse and prevalent defects in seven lead-poisoned men, appear to support and extend these views, but other interpretations must be considered. First, it is possible that the selection process—in the initial referral of patients or the self-selection for participation in the protocol—may have resulted in biasing our study group by inclusion of rare or unrelated endocrine or reproductive anomalies. Although such a bias may have influenced the prevalence of abnormalities in the group, it seems unlikely to be a major factor since most patients denied any sexual or reproductive complaint and none had undergone endocrine studies prior to referral or consenting to participate.

A second concern regards the possible confounding effects by diseases, habits, or environmental exposures other than lead. Only Case 2 was known to have a medical condition, diabetes mellitus, known to be associated with endocrinopathies. None had infections or anatomic abnormalities of the lower genital tract or histories of the same. None had contracted mumps orchitis. Only two were known to use alcohol to a significant degree (Cases 2 and 5) and no other significant habitual exposures or medication use were recognized

in the group. Occupationally, the patients came from six different sites and four job categories with no more than any two having common exposures other than lead. None had prior exposure to other environmental agents suspected to cause endocrine disease.<sup>17</sup>

A third possible interpretation of our data is that plasma or urinary lead interferes *in vitro* with some or all of the assays performed. This seems most unlikely in view of the lack of correlation between blood lead and measured effect. In fact, the most profound effects noted in the group were in the subjects with longest exposures but lowest lead levels. The absence of substantial changes after chelation therapy further rules out such an effect.

Finally, the coincidence of endocrinopathy with other features of lead intoxication raises the possibility that the abnormalities noted are nonspecific effects recently characterized in patients with chronic diseases including anorexia nervosa and renal failure.<sup>18-22</sup> Although our patients were ill, all were nutritionally intact and ambulatory. Except for patients 2 and 5 who had been disabled for several weeks, all were working regularly when seen. Renal dysfunction, though documented in three patients, was subclinical with clearances at least 60 ml/min in all. It appears likely therefore, that our results represent specific phenomena associated with lead poisoning.

Although the study group is small, sufficient data are available to partially characterize the lesions involved and contrast them with prior reports. Although *in vitro* and animal studies have suggested a primary effect of lead on thyroid uptake and organification of iodide,<sup>23,24</sup> the defects seen in three of our patients are more consistent with a central defect. The absolutely flat response to TRH stimulation in Case 7 is most consistent with pituitary dysfunction, while low thyroid indices, normal basal TSH values, and normal responses to TRH are consistent with partial hypothalamic or pituitary insufficiency. These findings lend further support to our prior report of central hypothyroidism associated with lead in brass foundrymen.<sup>6</sup>

Prior data on adrenal function in lead-poisoned men are limited to those reported by Sandstead who found subnormal urinary and plasma glucocorticoid responses to metapyrone challenge in 6 of 21 patients studied.<sup>5</sup> Our own results, demonstrating decreased urinary 17-hydroxycorticosteroids and blunted responses to challenges with insulin hypoglycemia and vasopressin, are supportive of a defect in the axis but are neither definitive nor localizing. The normal cortisol response to cortrosyn in Case 7, who had depressed responses to the other challenges, suggests a mild central lesion.

On the other hand, comparison of semen findings and testosterone levels with levels of pituitary hormones support a primary testicular effect on the gonadal-pituitary axis. While the level of involvement in those patients with oligospermia and normal FSH cannot be determined, high levels of serum gonadotropins in the azoospermic men exclude a primary pituitary or hypothalamic basis for gonadal failure. This interpretation is supported further by the findings of Leydig cell

hyperplasia on biopsies of these patients. This finding is in distinction to reports of depressed pituitary responses to clomiphene and gonadotropin releasing hormone by Braunstein et al.,<sup>4</sup> but consistent with the study of Lancranjan who found depressed sperm counts but normal levels of gonadotropins in urine.<sup>3</sup> In view of the central effects noted on thyroid and adrenal axes, and our failure to perform challenge tests of pituitary and hypothalamic gonadotropic responsiveness on all but Case 7, it is possible that both central and testicular lesions occur in some patients.

Regarding the natural history of these lesions, there are no reports, either in humans or animal model, prior to the fragmentary data presented here. Partial improvement in some parameters are evident in the four patients in whom blood lead levels were reduced to normal; germinal function, however, was not affected in the two azoospermic men. On the other hand, patient 4 who was treated but again exposed to excessive lead, showed a decline in sperm count and motility. Taken collectively, these findings suggest that the endocrine effects associated with lead intoxication other than complete azoospermia, may gradually resolve with treatment. However, confirmation of reversibility as well as demonstration of its time course and completeness will require further follow-up of these and other appropriately studied patients.

Finally, in view of the current controversy about low-dose effects of lead, it must be re-emphasized that all available literature on male endocrine function, including the present report, has focused on heavily exposed, largely symptomatic subjects. Whether these phenomena occur with reduced exposure or subclinical poisoning remain subjects for speculation. Further studies, directed at populations with blood lead levels consistently below 60 µg/dl, are required to explore the full dose-response of endocrine and reproductive organs to inorganic lead exposure.

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