CHAPTER 3

THE INHALATION OF PARTICULATE LEAD BY HEALTHY HUMAN SUBJECTS

The experiments outlined in this chapter were performed to determine the maximum concentration of atmospheric respirable inorganic lead particles that can be inhaled continuously throughout a lifetime by healthy persons without there being a demonstrably progressive accumulation of lead in their bodily tissues. The approach to this problem was patterned on the results of the balance experiments (intake of lead in food and beverages, and output in the feces and urine) described in Chapter 2. In the experiments described in this Chapter 3, human subjects whose lead metabolism had been observed under normal conditions inhaled air containing lead in a known concentration. The exposures were carried out over periods of time sufficient to demonstrate the occurrence or non-occurrence of a physiological response. It was postulated that the responses of human beings to continuous exposure of this type could be determined with approximate accuracy by extrapolation from the results of regular incremental increases in the duration of intermittent exposure, that is, x hours of exposure per day for a suitable time, followed by 2x, 3x, and 4x hours of exposure for comparable periods of time, will yield a series of points on a curve that can be extended to 24 hours per day, every day.

General Considerations

To determine the manner and extent of the exposure to lead of people in the general population (excluding persons involved in any recognized type of occupational exposure to lead), it appeared to be feasible to investigate the toxicity of a specific compound of inorganic lead administered in a small amount daily over a prolonged period of

time. Such an investigation appeared to call for the determination of the quantities of lead when ingested and when inhaled and the resulting toxic or subclinical effects. The separation of ingested and inhaled quantities of lead appeared to be advisable, if for no other reason than that the prevailing concept of occupational exposure to lead was that long-term lead inhalation caused lead poisoning.

We believed that the double-barreled problem of nonoccupational and occupational absorption of lead occurred through the combination of ingestion and inhalation. This concept led to the development of an experimental program wherein lead ingestion by subjects was quantified while the subjects inhaled inorganic lead in a known concentration within a respiratory chamber. The inhalation exposure followed a schedule patterned on the general practice of American industry. Experimental exposure was for 7.5 hours per day, with the remaining hours of the day being free from the experimental exposure. In addition, subjects did not enter the chamber on weekends. Experimental exposure took place over a prolonged period of weeks. Respiratory exposure to the ambient atmosphere (with its usual lead content) occurred when the subjects were not in the chamber.

The experimental program was designed to establish the effects of the following variables on the absorption and excretion of lead, its retention in the body during the period of exposure, and its loss from the body after exposure was terminated:

- concentration of lead in the atmosphere,
- size of the dispersed lead particles, and
- influence of the exposure duration (both per day and per week over prolonged exposure).

Inhalation Experiments 1 and 2 specifically addressed the effect that the concentration of airborne lead had on two subjects. Experiment 3 was designed to evaluate the influence that the lead particle size had on absorption, while Experiments 4, 5, 6, and 7 were conducted to verify the findings of Experiments 2 and 3. Experiments 8, 9, and 10 demonstrated the influence of exposure time on the quantity of absorbed lead. The next two experiments (11 and 12) were designed to determine the highest airborne lead concentration to which the subjects could be exposed continuously without incurring measurable increases in blood lead or urinary lead. Because the results of Experiments 11 and 12 were not conclusive, Experiments 13, 14, and 15 were carried out using a similar protocol. Discussions and results of these experiments are presented in this chapter according to the experimental numbers. With the exception of the details common to all 15 experiments, the protocols are summarized for each experiment in the following section.

We felt some concern when we were unable to identify the amount of absorbed lead resulting from the inhalation of lead and to separate it from the ingested lead. Likewise, for obvious reasons, we were unable to separate the results of the inhalation of a specific lead compound, within a specific period of time, from those results associated with the inhalation of the ambient atmosphere (with, perhaps, its multiplicity of inorganic lead compounds) during periods on the outside of the experimental chamber. However, we have presented the factual data to the best of our ability and have counted on the cooperation of our readers in accepting our limitations in dealing with living subjects.

The Development of a Respiratory Chamber

In preparation for the investigation of respiratory exposure to lead, a chamber was designed and built by L.B. Roberts, a member of the Laboratory staff at that time. This chamber was described and illustrated in a prior publication (2), but is more elaborately described herein. The design of the apparatus for introducing the desired streams of lead-bearing air into the chamber during the group of experiments is described in detail for those who may wish to reproduce, to consider critically, or to modify the experimental regimen. Details concerning the rationale for procedures are indicated in the protocol for the operation of the chamber as presented below.

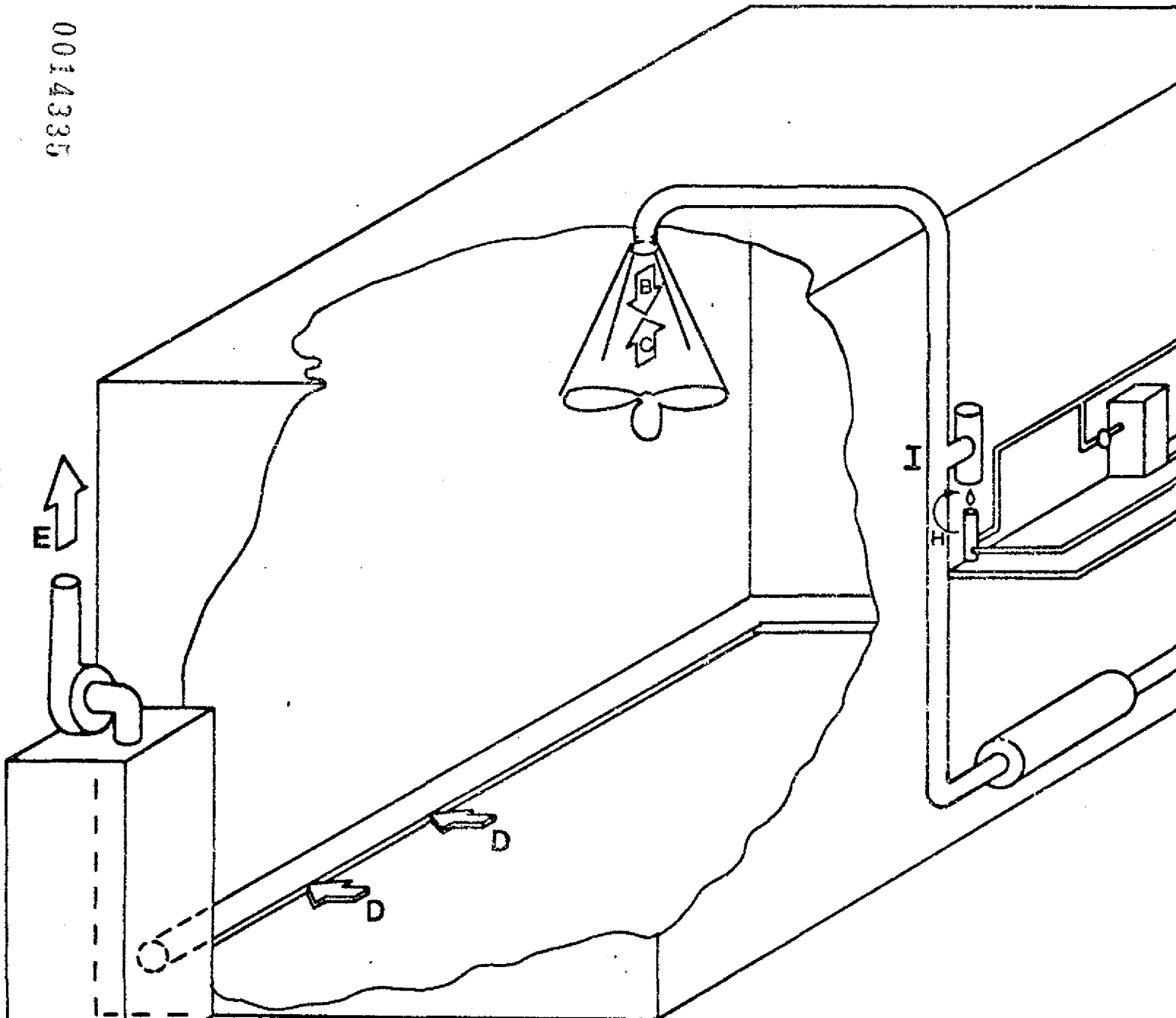
The Structure and Operation of the Respiratory Chamber

A chamber, 10 feet wide, 12 feet long, and 10 feet high, was constructed of double reinforced steel panels filled with glass wool insulation. After the panels were assembled, all joints were sealed with 4-inch, heavy-duty plastic tape. Two air locks were required, one for the entrance and exit of personnel and the other for the exchange of small objects or for direct communication. The outer opening of the chamber through which personnel entered was closed by a door with a positive lock, as used in refrigerators. The cement block wall of the air lock and the wall of the storage space used for cleaning equipment were painted with a synthetic resin and "papered" with overlapping, heavy-duty aluminum foil. The cement floor of the chamber was covered with heavy-duty linoleum. A drawing of the chamber is shown in Figure 3.1.

In order to minimize deposits of particulate lead within the distributing system of the chamber, the large tube (3 inches in diameter)

Figure 3.1

Scheme of Respiratory Chambers



that delivered the stream of lead-containing air had smooth bends and was kept completely unobstructed at the point of discharge near the ceiling of the chamber. A fan directed its counterstream of air upward, toward, and around the discharge end of the distributing tube at a rate sufficient to balance the incoming stream, thus scattering the incoming stream of air with a sufficient degree of uniformity throughout the chamber. The air in the chamber was discharged through appropriately distributed ports into a large duct situated around the inner wall of the chamber just above the level of the floor. Sampling ports were provided on three sides of the chamber to permit samples of air from the outside to be taken to the inside of the chamber. These ports were 1½-inch plated brass tubes which passed through openings cut in the metal walls of the chamber. The tubes were sealed in and flanged to prevent leakage. When not in use, they were closed with airtight, rubber caps, some of which were inside and some outside of the chamber. However, they could blow out or blow off if the pressure in the chamber became excessively high or low, as it would if either an intake or an exhaust pump malfunctioned.

The volume of this chamber was approximately 1,110 cubic feet. The chamber underwent a complete exchange of air in about three minutes, at a flow rate of 370 cubic feet per minute. An exhaust fan and an electrostatic precipitator removed particulate matter from the effluent stream of air leaving the chamber, the clean air then being discharged through an exhaust stack of the building.

As shown in Figure 3.1, air entered at "A" and was impelled through a sound muffler to the orifice at "B" and thus into the chamber, having picked up, via the venturi at "I," the products of combustion at

"H." A stream of propane, entering the meter at "G," was joined in the burner by a measured stream of air, a measured portion of which had passed through an armored flask over a small quantity of tetraethyllead dissolved in dodecane. The combustion resulted in the quantitative conversion of tetraethyllead to lead sesquioxide. The stream entering the chamber was met by a countercurrent of air from the fan at "C" and was thus distributed. The mixed air of the chamber was withdrawn through properly spaced ports "D" in the large duct around the inside base of the chamber, and through the electrostatic precipitator by the balanced exhaust blower at "E," from which it entered a large vertical stack. "B" was the exit of a four-inch pipe that had an exit velocity of approximately 4,000 cubic feet per minute. The air entered the chamber at approximately 300 cubic feet per minute at orifice "B" and was removed at points "D" at the same rate.

Somewhat later, shortly after the initiation of experimental work involving respiratory exposure to lead, it appeared to be advantageous to conduct certain of the experiments in parallel, i.e., to employ two subjects, simultaneously, under essentially comparable conditions. For this reason, a second chamber, similar to the first but smaller, was constructed in the same large room as the first. This second chamber was 930 cubic feet in volume, and had a throughput of air of about 235 cubic feet per minute,with a complete air exchange in approximately four minutes.

The availability of two respiratory chambers made it possible to exclude all but specific compounds of lead for experimental inhalation

in the chamber. The combustion of tetraethyllead under suitable conditions appeared* to allow the introduction of an essentially specific inorganic lead compound (of approximately the same sized particles) into the respiratory chamber. It was believed* that the compound was lead sesquioxide (Pb_2O_3) in substantially pure form.

The lead sesquioxide, as referred to in foregoing comments, owed its prominence in this investigation to two characteristics. First, it was believed* to be the lead compound that is the principal result in automobiles of the combustion of gasoline containing tetraethyllead. This apparent fact concerning lead sesquioxide was reason enough to have given it prominence in the public mind. Second, it was also readily produced in substantially pure form, and was thus convenient as a specific lead compound for investigation.

The lead particulate generation procedure consisted of passing a stream of air through an armored flask containing a small quantity of tetraethyllead in dodecane, and then into the flame of a small Bunsen burner fueled by propane. The products of combustion were introduced into the venturi and on into the respiratory chamber. An insignificant quantity of carbon dioxide (no carbon monoxide) was detected in numerous tests of the chamber.

The particles of lead sesquioxide produced by this procedure were 0.05 micron in diameter. It was not feasible at the time to produce

*On inquiry of analytical experts as to the precise available results concerning the combustion of tetraethyllead, there is not complete agreement as to the technical minutiae of the chemical by-products of the process. To the extent that the editorial novice in these matters is entitled to any opinion, the "apparent fact" is not far from the truth, and is therefore accepted as such.

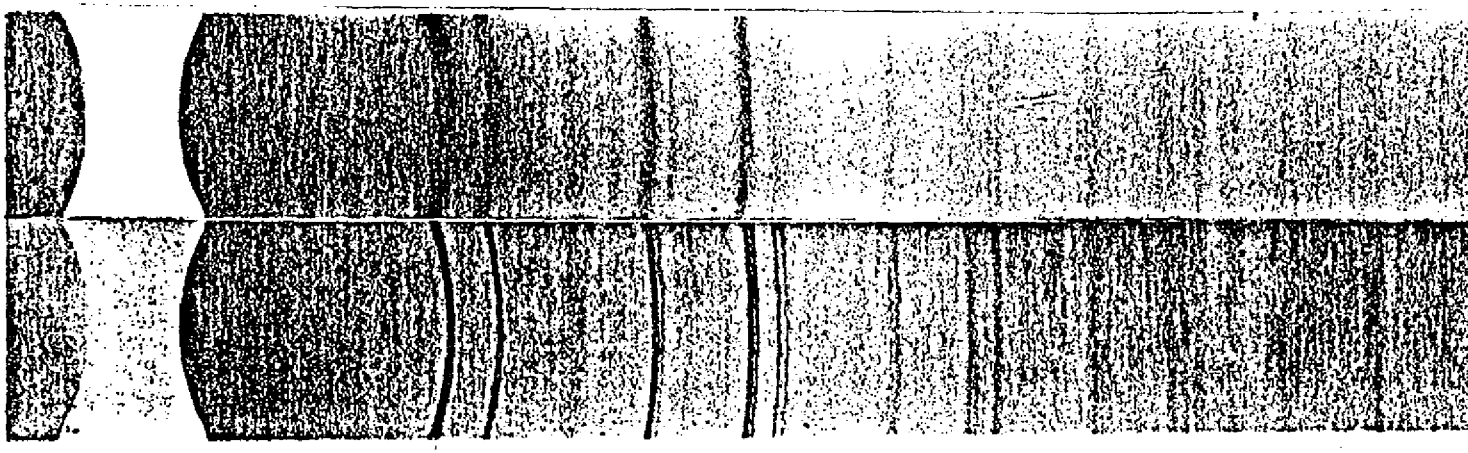
particles of considerably increased size by this method, so another method was sought. The methods and equipment that were employed are discussed in some detail below.

Lead dioxide was also converted to the sesquioxide by the following simple process. In a shallow aluminum pan, with occasional stirring, commercial lead dioxide was heated in a muffle furnace for about 72 hours at 350°C. It was converted completely to lead sesquioxide, as determined by its X-ray diffraction pattern (Figure 3.2). We employed lead sesquioxide obtained in this manner in several of the experimental programs in which individual subjects underwent exposure to specific concentrations in air for various periods of time. During such periods, subjects were exposed to atmospheres containing lead sesquioxide in particulate sizes varying from 0.05 micron up to 1.2 microns. These generated atmospheres were distributed, in specific cases, to include large, intermediate, or minute particles. By such means, the effects of the size of particles on their gross behavior in the respiratory and alimentary tracts were perceived.

To produce lead particles of varied size up to 0.9 micron in diameter for some of the experiments, a third method was employed. After being ground finely in a ball mill, a weighed portion of the sesquioxide was mixed in acetone to make a slurry, which was introduced on the inner surface of an aluminum tube 1½ inches in diameter and 6 inches in length. This tube was rotated horizontally while the acetone evaporated, leaving a thin uniform coating of lead sesquioxide. The coated tube was then inserted over the motor-driven head and body of a generator which was designed by Waldo Younker, a staff member of the Laboratory at that time. As the hollow generator rotated and retracted within the coated tube,

FIGURE 3.2

Comparison of X-ray Diffraction Patterns



A shows the particles in the air of a respiratory chamber occupied by

B shows lead sesquioxide as indicated in the literature.

A and B are obviously identical despite differences in their individua

a jet of air was passed at an angle through the tube's center and through its head, cutting a thin line of lead sesquioxide from the coating. This stream of air was directed into a series of cyclone particle separators, into the venturi, and then into the chamber. This equipment is shown in Figures 3.3 and 3.4.

In other experiments, the apparatus containing the coated tube was mounted vertically and a phonograph needle was situated on the head of the generator. As the tube was rotated and retracted, the needle cut off the coating in chunks from the enclosing tube. The particles fed into the main stream of the chamber. Figures 3.5 is a photomicrograph of particles precipitated from the atmosphere of a respiratory chamber during the course of an experiment.

Additional features of the location and the operation of the Laboratory respiratory chamber are discussed in the paragraphs below.

1. Location and Operation

Since this experimental program had to be conducted in the same building (although on a separate floor) that housed the analytical facilities, it was essential that the respiratory chambers and equipment be physically separated from the analytical facilities. Moreover, the chambers and their operations could not be permitted to become a significant source of lead contamination of the air on the inside or outside of the Laboratory building. Rules were established and posted regarding access to the experimental area. The schedules for bathing and donning clean clothing were arranged to protect the subject against spurious contamination, as well as to prevent contamination of other areas of the Laboratory building. The air lock used for the introduction of materials and for the entrance to and exit from the chamber by a subject was designed to minimize the possibility of spreading contamination from the chamber. The electrostatic precipitator, on the discharge line from the chamber, operating at low load, effectively removed particulate lead from the effluent stream of air, thus preventing significant contamination of the outside air.

Figure 3.3

Lead Particle Generator

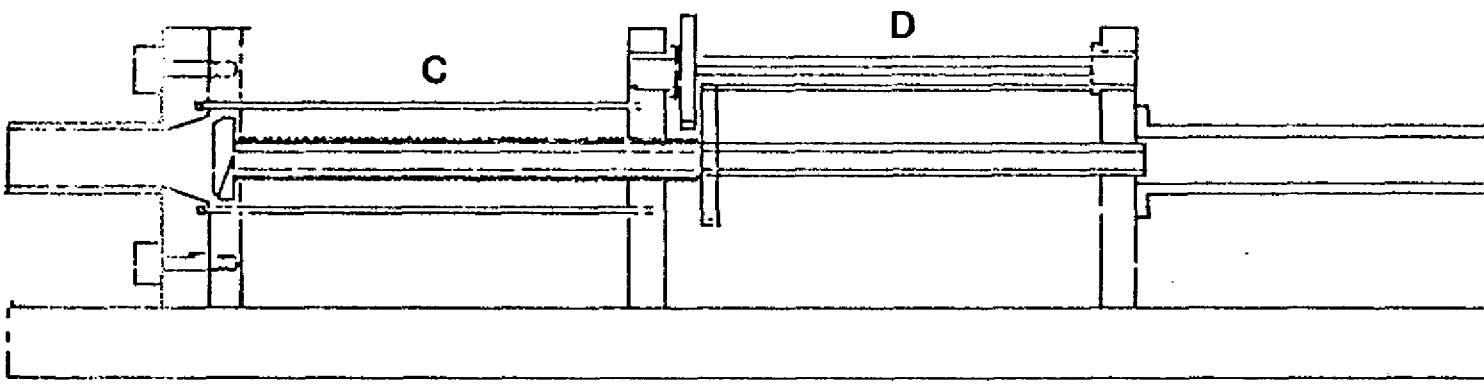


Figure 3.4

A Cross-Section of the Lead Particle Generator

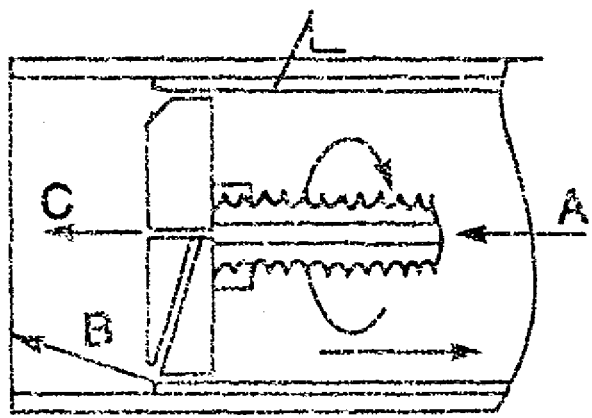
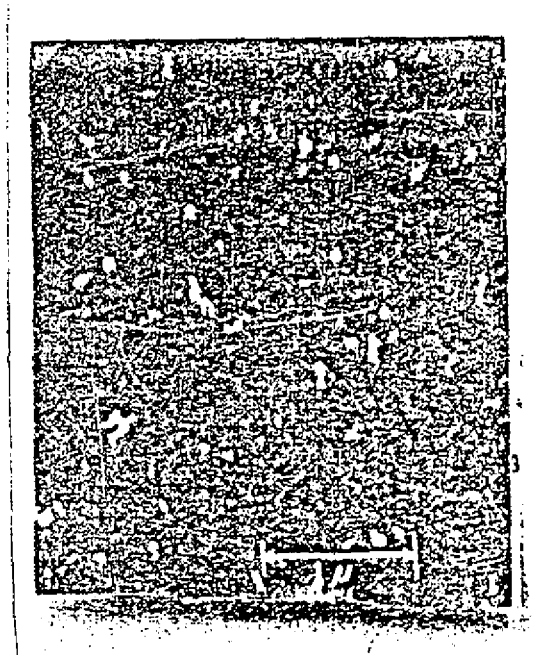


FIGURE 3.5

Lead Particles Precipitated from the Respiratory Chamber



2. Plan of Area

To achieve strict control of conditions required for long-term experimentation, it was clear that the three essential spaces, the chamber, the service area, and the change area, should be continuous. No real or apparent crowding or misuse of the chamber itself was considered to be acceptable. The concept of a "room within a room" evolved, and a "room" sufficiently large to accommodate two generously proportioned chambers and associated facilities was found. This room also met the requirements for remoteness from the analytical facilities mentioned previously. Matters of lighting, heating, cooling, quietness, outside visibility, the intake and discharge of air, and the location of plumbing, together with considerations for efficient operation, comfort, convenience, and safety, dictated the final plan for locating the chambers in the room. One chamber side abutted on a wall of the large room, while three sides were readily accessible. Adequate space remained in the large room for lockers, shower stalls, and storage facilities.

3. Other Features of the Respiratory Chambers

After complete safety, there is nothing more important in any human experimentation than the morale of the experimental subjects, especially in a prolonged investigation. Since morale is affected by physical surroundings, it was considered essential to design the surroundings to be pleasant and comfortable. The size of the chamber allowed the subject to move about freely, and provided space for a desk, chairs, a telephone, and a work bench. The air inside the chamber was conditioned and maintained at a comfortable temperature. Fluorescent light from light panels above the ceiling of the chamber provided ample illumination. The placing of the lights on the outside of the chamber prevented the heat load of lamps from being added to that of the chamber. The level of noise was kept low in the chamber; the air flowing through at a low rate, although at a somewhat higher throughput of air than that of air conditioning, was controlled by quiet blowers and fans and the use of mufflers. Wide doors allowed large pieces of furniture or equipment to be moved in or out.

General Protocol of the Inhalation Experiments

The chamber operator, who was on duty every day to ensure the continued and proper operation of the chamber, began each day's activities by starting the blower and fans, checking and starting the generating and recovery equipment for the lead compound, and making necessary adjustments to ensure the desired concentration of lead in the chambers.

Meanwhile, the subjects changed from street clothing to the clothing to be worn in the chamber. Separate lockers were provided for storing street and chamber clothing. After checking with the operator, the subjects entered the chamber through the air lock. They then proceeded with the day's work, which included routine housekeeping chores, principally cleaning, productive office work, and routine collection of air samples within the chamber.

To minimize the possibility of spreading particulate lead into other areas of the Laboratory, when the subjects left the chamber for lunch within the Laboratory, they stopped in the air locks on the way out and put on laboratory coats and slippers that were stored in a locker in the air lock. Before and during lunch, the subjects took precautions to prevent lead contamination of food, urine, and fecal samples.

At the end of the day's work, the subjects reversed the morning's procedure, took showers before donning street clothing, and left. Each subject kept records of the duration of his lead exposure by noting the time of entrance into and the time of departure from the chamber.

The operator of the chamber also reversed his procedures of the morning by stopping the fan, the blower, and the generating equipment. He then made the necessary provisions for the operations of the next day, and secured the chamber for the night.

In the respiratory chamber inhalation experiments, which were conducted from 1950 to 1970, 12 individuals were exposed to various preparations of particulate lead sesquioxide in concentrations ranging from 5 to 150.0 micrograms per cubic meter of air for varying periods of time. Table 3.1 summarizes some of the pertinent characteristics of the subjects and their exposure to lead.

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TABLE 3.1

CHARACTERISTICS OF SUBJECTS AND THEIR INHALATION EXPOSURES

Experiment Number	Subject's Initials	Age at Experiment Initiation	Sex	Race	Control Periods		Exposure Periods					
					Dates	No. Wks.	Dates	No. Wks.	No. Days/Wk. in Chamber	No. Hr./Wk. in Chamber	Pb Concentration (μ/m^3)	Pb Particle si (μ)
1	M.O.B.$_1$	28	M	Black	4/50-12/50	37	1/51-12/52	102	5	7½	73	50%<0. 90%<0.
2	F.C.$_1$	29	M	Cauc.	6/51-12/52	80	4/53-12/54	88	5	7½	153	50%<0. 90%<0.
3	F.C.$_2$	32			12/54-9/56	89	9/56-9/57	52	5	7½	147	50%<0. 90%<2. max =
4	M.B.	42	M	Black	1/55-6/55	20	7/55-5/56	48	5	7½	151	50%<0. 90%<1.
5	M.O.B.$_2$	34			1/56-3/56	11	3/56-4/57	56	5	7½	147	50%<1. 90%<6. max =
6	J.S.	55	M	Cauc.	5/57-10/57	20	10/57-11/59	112	5	7½	147	50%<1. 90%<5. max =1.
7	P.B.	37	F	Black	5/70-1/71	33	1/71-8/71	33	5	7½	148	50%<0. 90%<0.
8	S.B.	25	M	Cauc.	1/59-1/60	56	1/60-6/61	72	5	4 8 10	151.3	50%<0. 90%<0.
9	L.D.	33	M	Cauc.	3/60-12/61	91	12/61-3/62	16	*	3	148	50%<0.
							3/62-7/62	16	*	6		90%<0.
							7/62-11/62	16	*	9		
							11/62-2/63	16	*	12		
10	Jo.S.	32	M	Cauc.	10/60-12/61	59	12/61-3/62	16	*	3	150	50%<0.
							3/62-7/62	16	*	6		90%<0.
							7/62-11/62	16	*	9		
							11/62-2/63	16	*	12		
11	N.K.	50	M	Cauc.	3/63-10/63	29	10/63-7/64	36	*	6	9.9	50%<0.
							7/64-11/64	16	*	9		90%<0.
							11/64-3/65	16	*	12		
							3/65-11/65	32	*	8 3/4		
							11/65-2/66	16	*	12 3/4		
12	S.S.$_1$	25	M	Cauc.	10/63-2/64	16	2/64-8/64	24	*	3	9.9	50% <0
							8/64-12/64	16	*	6		90% <0
							12/64-8/65	32	*	9		
							8/65-2/66	24	*	8-3/4		
							2/66-7/66	20	*	12¼		
13	S.S.$_2$	27			7/66-10/66	13	10/66-2/67	16	*	3¼	19.6	50% <0
							2/67-10/68	80	*	5¼		90% <0.
14	H.R.	22	M	Cauc.	4/66-10/66	24	10/66-1/67	12	6	3¼	19.8	50% <0.
							1/67-6/67	20	6	5¼		90% <0.
							6/67-8/67	9	6	16¼		
15	D.H.	23	M	Cauc.	11/67-7/68	35	7/68-11/68	16	6	8	21.1	50% <0.
							11/68-2/69	16	6	10		90% <0.
							2/69-6/69	16	6	12		
							6/69-10/69	16	6	14		

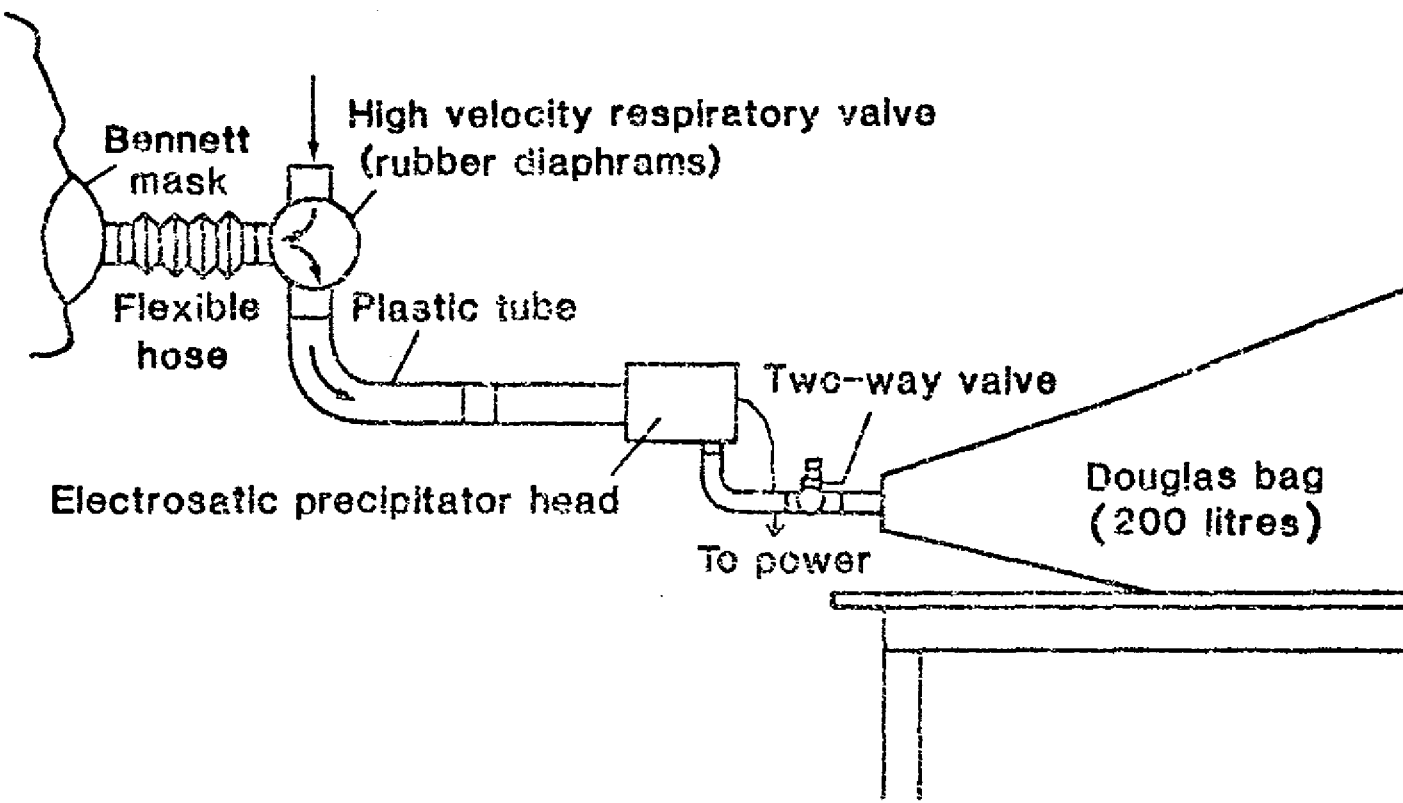
To measure the quantities of lead retained in the lungs of the lead inhalation subjects, the subjects breathed the respiratory chamber air through a two-way mask and exhaled through an electrostatic precipitator into a Douglas bag until the desired volume of air had been collected. The Douglas bag apparatus is illustrated in Figure 3.6

Admittedly, measuring lead retention was a formidable task. It was by no means certain that it could be measured accurately since the subject would have to breathe as though responding only to the customary physiological stimulus. He had to do this long enough and carefully enough so that respiration was excessively distorted because of some degree of discomfort. What we wished to determine was the extent of the retention of lead in the lungs during the inhalation of the atmosphere of the chamber. It is probable that the only satisfactory evidence of the occurrence or the extent of the lead absorption from this source was provided, indirectly, by the rate of the excretion of lead in the urine voided during the physiologically corresponding period of time, or, perhaps, by the concentration of lead in the blood, as compared with the values of a preceeding period.

The measurements of the volume and the lead content of the residual air in the Douglas bag were related to the original lead content of the respired air in the chamber and the time involved in collecting the air in the bag. On the basis of repeated performances of apparently adapted subjects, together with subsequent determinations of the volume and the lead content of their urine, and the concentration of lead in their blood, the approximate extent of the absorption of lead in the lungs following inhalation could be estimated.

Figure 3.6

Illustration of Equipment Used to Determine Lead Content of Expired Air



The concentration of lead measured in the chamber air minus the concentration found in the exhaled air was expressed as a percentage of the inhaled lead. As an example of the calculations, one subject exhaled 414 liters in 20 minutes. The chamber concentration was 0.194 mg lead/m^3 air.

$$\frac{414}{20} = 20.7 \text{ liters per minute, breathing rate.}$$

$$\frac{(0.194 - 0.0845) \times 100}{0.194} = 56.4\% \text{ retention.}$$

Table 3.2 presents summaries of the results of these tests. The high variability between subjects and in the same subject from day to day is shown in the range. This may indicate the impossibility of a subject's ability to control the rate and depth of respiration, especially in this experimental situation. Using these results, calculations of the total lead retained can be assumed to give only a "ball park" result. Therefore, changes in the concentrations of lead in the blood and in the amount of lead in the urine are a better indicator of the level of exposure.

This test of retention was not successfully performed when the subject breathed normal ambient air at the Laboratory. If a subject breathed 10 liters per minute of air containing 0.005 mg lead/m^3 air and retained 50%, he would retain 36 micrograms of lead per day. Using the average breathing rate and percent retention given in Table 3.2, 45 micrograms of lead would be retained per day from air containing 0.005 mg lead/m^3 air. Using the averages for Subject F.C. in the same way gives 41 micrograms. Since subjects breathed air at the Laboratory and elsewhere during their control periods, it is likely that the average concentration was somewhat lower than the 0.005 mg lead/m^3 air used in the calculations.

TABLE 3.2

ESTIMATED LEAD RETENTION OF INHALATION EXPERIMENTAL SUBJECTS

Subject	Chamber Conc. (mg Pb/m^3)	Breathing Rate (l/min)	Percent Average	Retention of Lead Range
M.O.B.$_1$	0.073	9.6	37.0	17.6 - 44.0
F.C.$_1$	0.153	10.3	36.0	19.3 - 48.5
M.B.	0.151	14.9	54.1	38.7 - 69.0
M.O.B.$_2$	0.147	11.8	53.3	24.4 - 64.0
F.C.$_2$	0.147	17.3	43.0	20.6 - 50.5
Ju.S.	0.147	15.7	44.9	11.8 - 72.5
S.B.	0.151	18.4	34.2	16.3 - 45.2
L.D.	0.148	19.9	39.2	28.7 - 49.3
Jo.S.	0.150	17.6	33.5	20.4 - 48.2
N.K.	0.010	10.5	59.6	53.5 - 66.0
S.S.$_1$	0.010	16.0	49.1	24.0 - 69.0
S.S.$_2$	0.020	9.2	52.3	21.3 - 73.8
H.R.	0.020	8.4	67.2	35.5 - 79.6
D.H.	0.021	9.7	52.5	17.2 - 74.4
P.B.	0.148	9.6	51.9	18.4 - 74.5
Average		13.3	47.2	

1 - First exposure period.

2 - Second exposure period.

INHALATION EXPERIMENTS 1 AND 2
(May 1950 through September 1956)

Protocol

The first subject in the study of various aspects of lead inhalation was a 26-year-old male, designated as M.O.B. The normal lead metabolism of Subject M.O.B. was followed for 36 weeks, after which his exposure to particles of lead sesquioxide of a mean diameter of 0.05 micrograms at a concentration equivalent to 0.075 mg lead/m^3 air was begun. Exposure in the chamber continued for approximately 7.5 hours per day, time being recorded precisely each day, on 5 days of each week for 92 weeks.

After termination of the experimental exposure to lead, the clinical and chemical observations were continued for an additional period of 148 weeks. Prior to the end of this post-exposure period, the subject's bodily lead content and his current lead metabolism were believed to have returned to the initial (pre-experimental) state. This first experiment, which was conducted continuously over a period of almost 5.3 years with only brief periods of respite for the subject, but none during the period of exposure, was used as a pilot study for subsequent details of experimental design while serving to demonstrate the response of one level of dosage.

In the second experiment, Subject F.C. was followed in a preliminary manner, as described, for 76 weeks, which was longer than had been intended due to the prolonged exposure of Subject M.O.B. within the only chamber available at that time. After F.C.'s control period, he entered the chamber on the schedule outlined above. The same exposure conditions as those of the first experiment were used. The resulting concentration, equivalent to 0.15 mg lead/m^3 air, was based on the

occupational standard generally advocated at that time by industrial hygienists in the United States.

The period of exposure under the above conditions was 88 weeks, after which the observations on this subject were continued for a post-exposure period of 130 weeks, and beyond the 76 weeks indicated in the following figures.

Discussions and Results of Inhalation Experiments 1 and 2

The results of these first two experiments are shown in a series of graphs. In the first pair of graphs (Figure 3.7, Subject M.O.B., and Figure 3.8, Subject F.C.), the lower line shows the mean daily weight of the ingested food and beverage (exclusive of drinking water), as calculated from the data of each day in every 28-day period. As indicated, the upper intertwining curves represent the mean daily intake of lead from food and all beverages, including drinking water, and the mean daily output of lead in the feces only. Both of these values were calculated for each 28-day period from the analytical data representative of each day. Each point on each curve represents the mean value (weighted average) of 28 determinations.

Many interesting features of these findings can be noted, i.e., the lead in the feces bore the same relationship to the lead in the food during the periods of the respiratory exposure of the two subjects just as it did in the control and post-exposure periods, demonstrating that lead was caught in the upper respiratory tract and was subsequently swallowed. As we look at the other charts, which give evidence of an increase in the absorption of lead during the period of respiratory exposure, it is clear that similar absorption took place in the lungs of the subjects. The proportion of the inhaled lead that was entrapped in the lungs of

Figure 3.7

Alimentary Intake and Output of Subject M.O.B

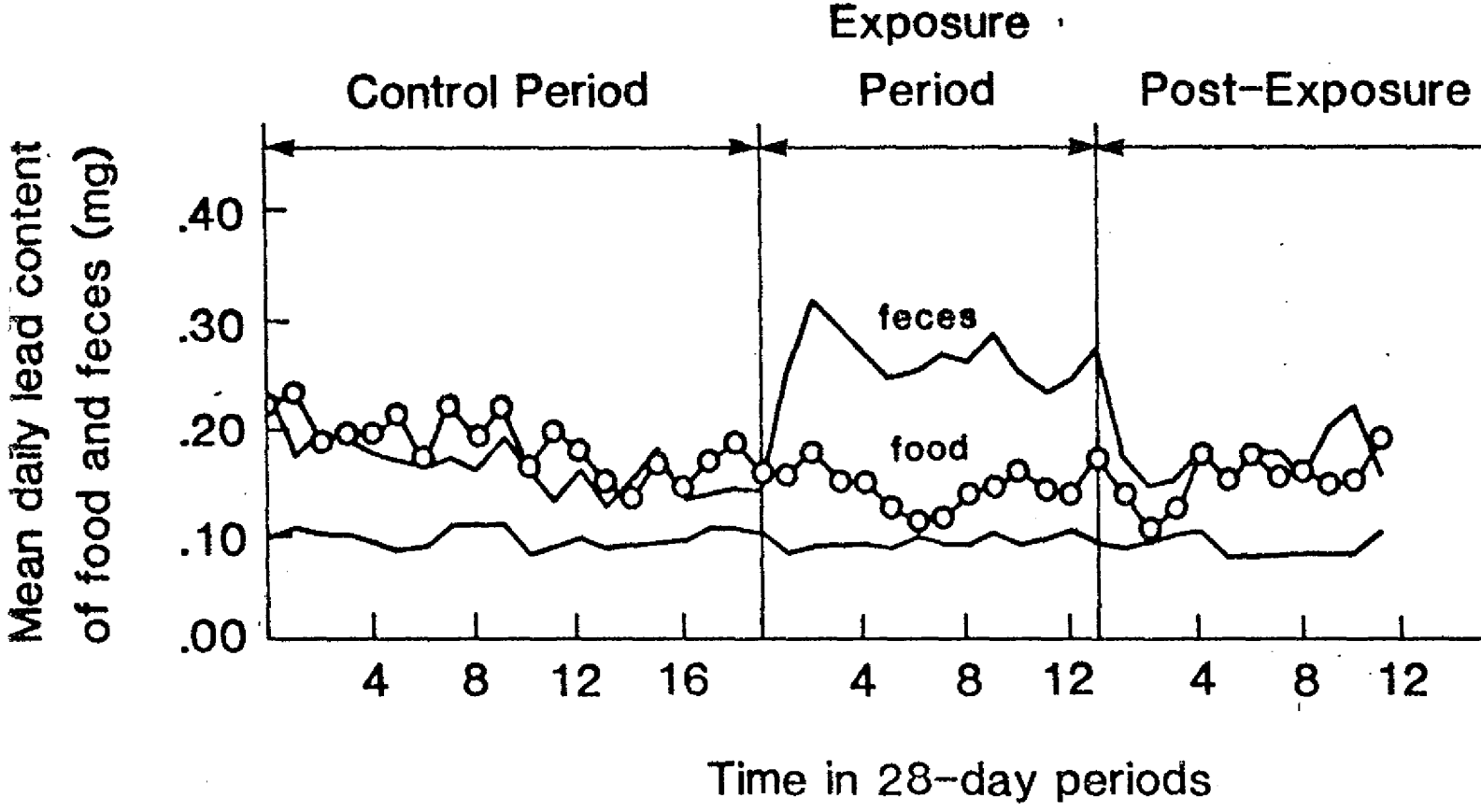
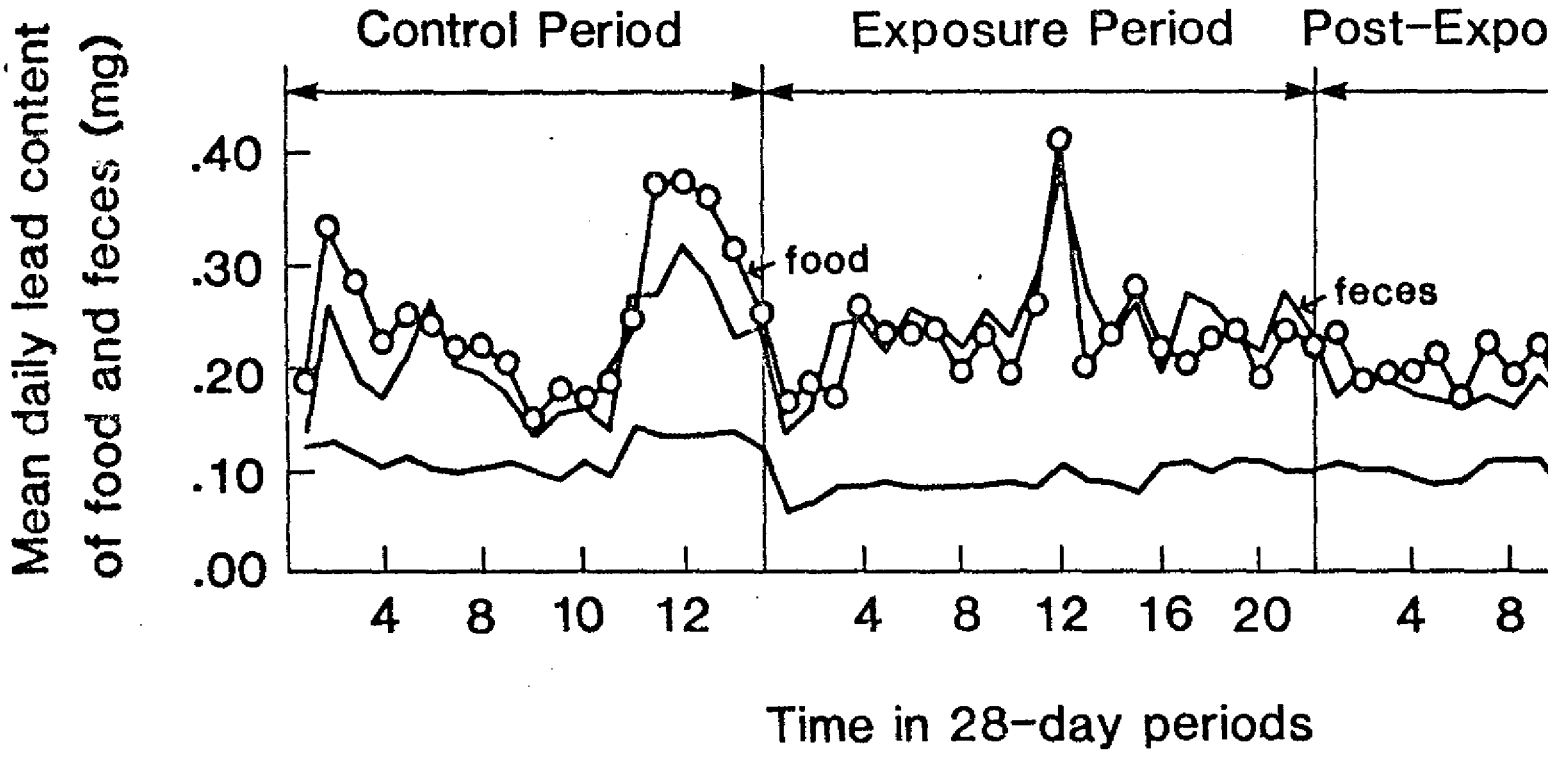


Figure 3.8

Alimentary Intake and Output of Subject F



the two subjects varied somewhat from time to time. However, many determinations of the proportion retained in the lungs of Subjects M.O.B. and F.C. during respiration within the chamber averaged 37 and 36 percent, respectively.

One other point is worthy of comment as background information for the proper interpretation of later charts. Careful scrutiny of Figures 3.7 and 3.8 reveals some fairly wide variations in the intake of lead from the food from time to time. It is noteworthy that these variations parallel, and are clearly responsible for, almost all of the variations in the lead content of the feces. Most of the lead ingested in the food is evacuated unabsorbed with the feces, as we have demonstrated in the ingestion experiments described in Chapter 2. Nevertheless almost every increase or decrease in the lead intake from food is accompanied by a corresponding increase or decrease in the urinary excretion of lead. It is important to remember this in connection with the variability of the urinary excretion under the conditions of an essentially constant level of experimental respiratory exposure to lead. In short, the lead taken in daily with food is an important factor in the daily output of lead in the urine. This factor must be kept in mind constantly in any appraisal of the significance of the urinary excretion of lead.

The daily intake of lead in the food of the individuals varies with the type and quantity of food consumed; it varies, then, with the dietary habits and the appetite, with the seasons, with the home life (cuisine), and with the locale of the individual subject or subjects. For example, Subject F.C. changed his boarding house in the fourteenth month of the control period, resulting in the somewhat unusual proportions indicated at that point in Figure 3.8. It may be noted that the weight

of the food increased, probably because of enhanced appetite at this time, and that it decreased some five months later because of familiarity with the no-longer-new dietary regime. The lead in food and feces decreased correspondingly. These influences are reflected in Figures 3.8 and 3.9, in which the sharp upturn and falling off of the urinary lead output and concentration would otherwise be disconcerting. Because of this and other apparent vagaries in the urinary lead excretion of this subject from time to time, the curves of the lead content of the food in the control period and that of both food and feces in the other two periods have been repeated in Figure 3.9.

In Figures 3.10 and 3.11, the mean daily urinary output of lead for the two subjects is plotted with the mean daily volume of the urine voided for each 28 days of the entire experimental period. The lower dotted line shows the mean daily volume of the urine voided, as calculated from the measurement of the volume each day over each period of 28 days on the scale indicated on the right. The upper dotted line represents the mean daily lead content of the urine voided, as similarly calculated. The peaks correspond, not precisely but generally, with an increase in the lead content of the food and feces (Figure 3.7 and 3.8). The peak at the 19th point of the exposure period in Figure 3.7 (after "equilibrium" has been attained) corresponds in time with a sharp increase in the lead content of the feces, which is approximately duplicated in the lead content of the food. It must be kept in mind that these points are the weighted averages of 28 determinations and not the result of a single error of sampling, contamination, or analysis.

In Figure 3.11, note the "overshooting" of the response to exposure (5th and 6th points during the period of exposure) as in Figure 3.10,

Figure 3.9

Concentration of Lead in the Urine
Mean Daily Lead Content of Food and Feces
Subject F.C.

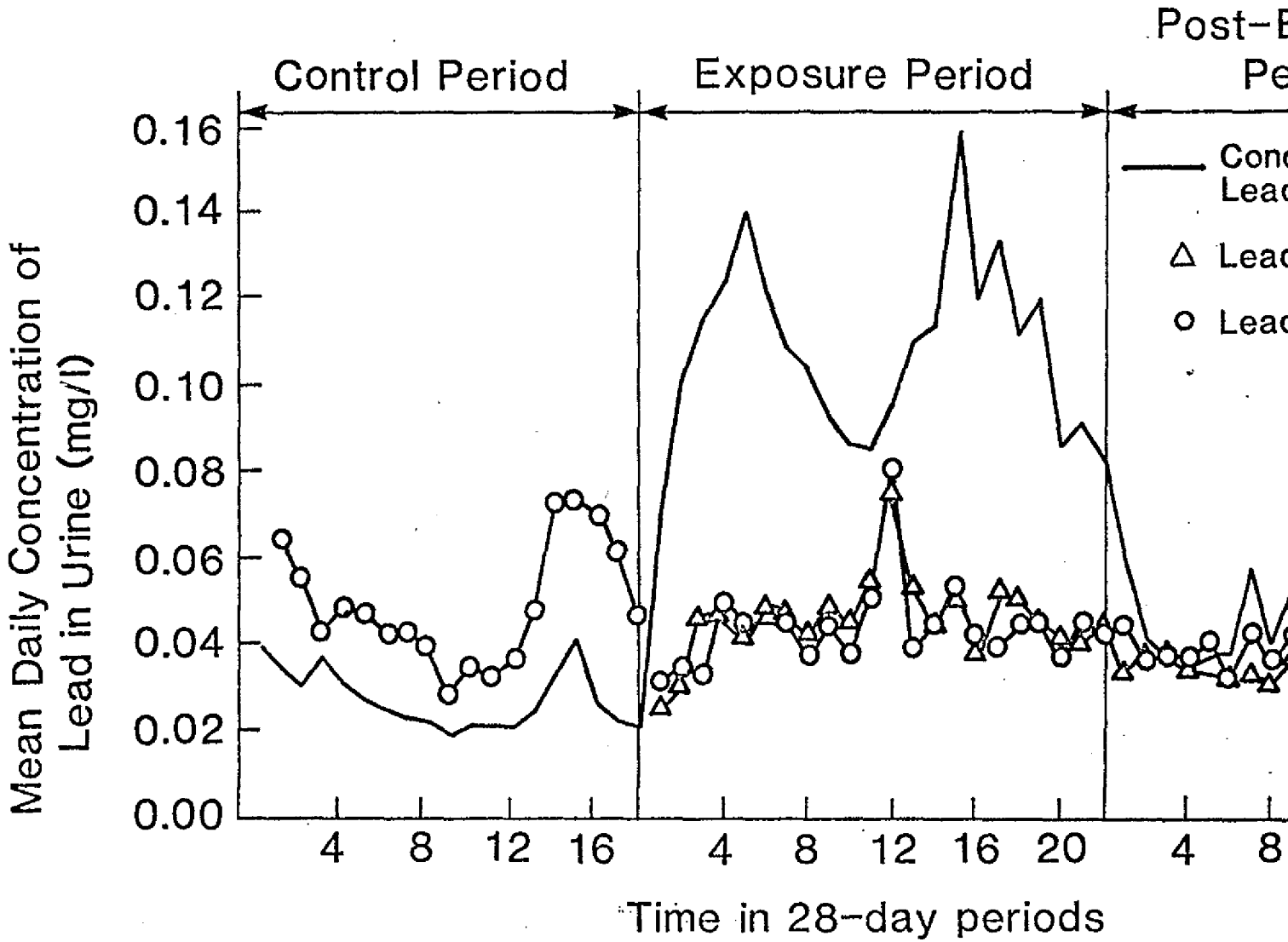


Figure 3.10

Mean Daily Urinary Output of Lead of Subject M.O

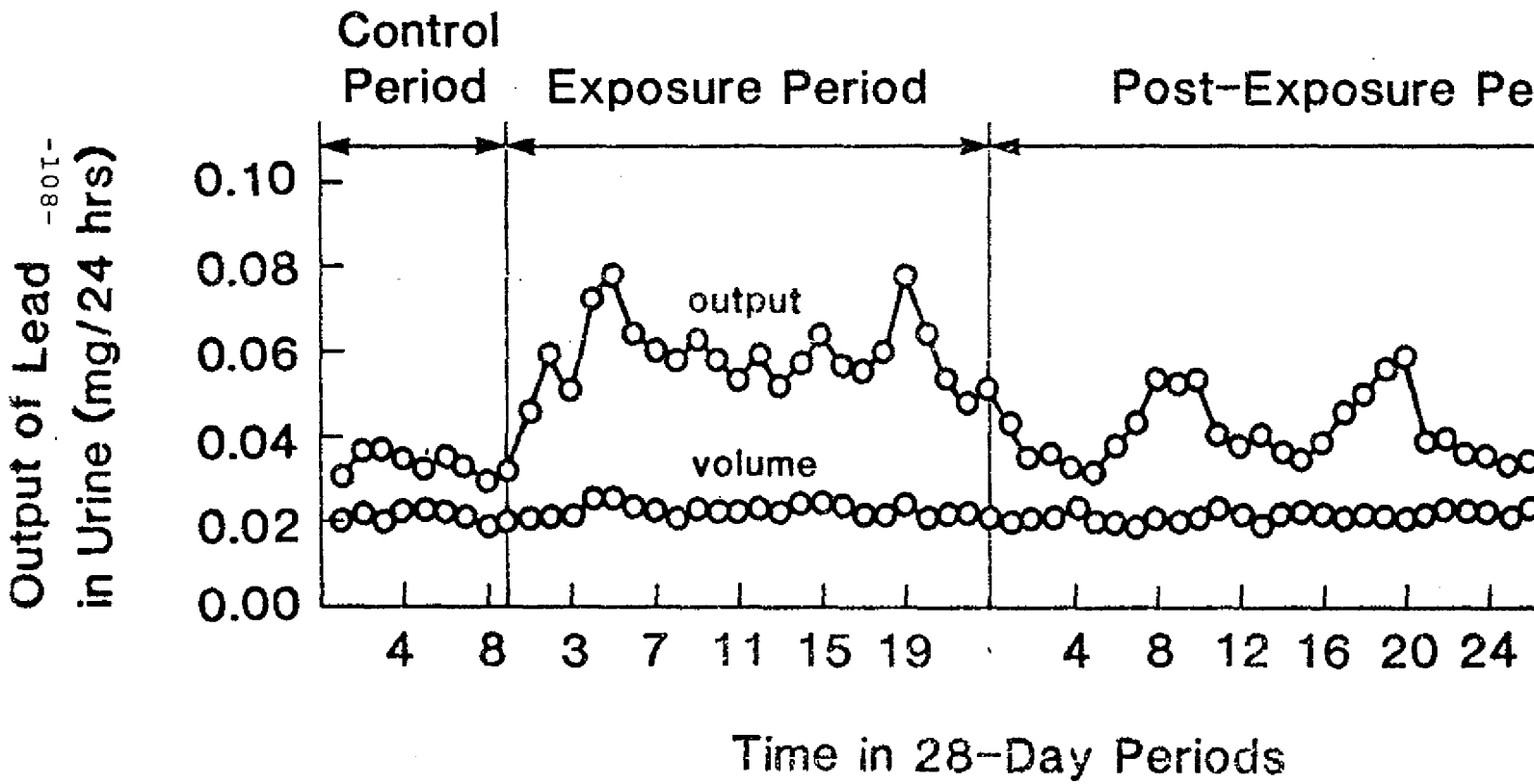
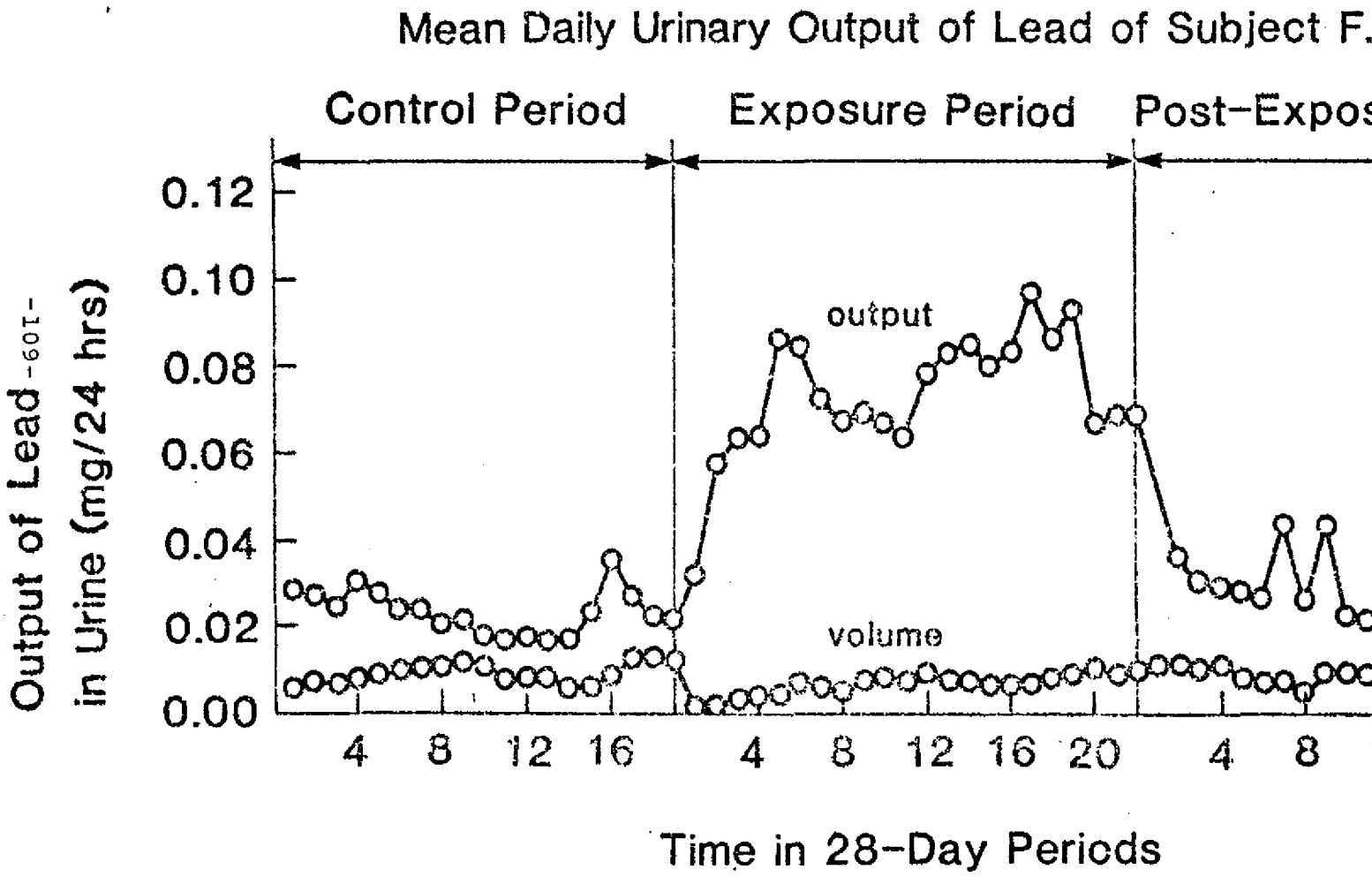


Figure 3.11


Mean Daily Urinary Output of Lead of Subject F.
Control Period
Exposure Period
Post-Expos
Output of Lead -109- in Urine (mg/24 hrs)
0.12
0.10
0.08
0.06
0.04
0.02
0.00
output
volume
4
8
12
16
4
8
12
16
20
4
8
Time in 28-Day Periods

without a corresponding peak in food and feces (Figure 3.8). Note also the consistently low volume of the urine of Subject F.C., the especially low volume during the early part of the period of exposure (hot weather), and the higher variability, as compared to that of Subject M.O.B., throughout the experiment.

Aside from the influence of ingested lead, several points of outstanding significance are revealed. First is the fact that the responses of both subjects to the experimental exposure were the same qualitatively, i.e., the urinary output of lead increased with equivalent promptness (at a somewhat more rapid rate in response to the larger dosage); it rose to a relatively high point in both instances, receded appreciably, and then leveled out (with appreciable variations, inconsistent in direction) to maintain an essentially horizontal curve, the level of which was well above the normal (control) base line. The horizontal character of these curves, developed after six (Subject M.O.B.) to nine (Subject F.C.) months of exposure, varied sharply from the maintained upward slopes of the curves representing the urinary output of subjects to whom lead was administered daily along with their food. This variation was not unexpected but was gratifying in view of the corresponding behavior of men employed in industries where lead exposure is fairly constant. We have observed, repeatedly, that individuals and groups of such employees reach a level of urinary lead excretion that characterizes the severity of their exposure. Further, this level changes little thereafter for years, within the limits of physiological variability, except in response to an increase or decrease in the severity of the exposure to lead. This, no doubt, is due to the intermittent exposure to and absorption of lead in association with the relative lack of exposure during 16 or 16.5 hours of each working

day and during the two days each weekend. During a large part of these periods of low exposure, an individual's output of lead is greater than the intake. Thus, a point of balance is reached which is dependent on both the time relationship and the dosage.

Reference to dosage leads to the second point of importance in these two subjects. The level at which equilibrium was reached varied directly with the concentration of lead in the air that they breathed. The two subjects started from slightly but significantly different baselines. In accord with his lower output and intake of water, Subject F.C. had a lower base level of lead output than did Subject M.O.B. However, the mean daily output of lead by Subject M.O.B. at equilibrium was 0.055 milligram, and that of Subject F.C. (at twice the concentration of lead in his respired air) was 0.070 milligram at equilibrium.

A third point to be noted is that in neither instance did the respiratory exposure of the subjects to lead result in a consistent increase in their urinary output of lead to a level that could be regarded as even approaching the threshold of danger. This point will be emphasized in the presentation and discussion of further data.

Since the urinary excretion of lead by industrial employees is expressed more conveniently and, under suitable conditions of sampling, somewhat more satisfactorily in terms of urinary lead concentration rather than of lead output per unit of time, the data have been so represented in Figures 3.9 and 3.10.

In Figure 3.9, the single line without dots portrays the deviation in the mean daily concentration of lead in the urine, as plotted with lead ingested in food during the control period, and with that of both food and feces during the remaining periods of the experiments.

This then shows the influence of the alimentary lead on the urinary excretion of lead. In this figure the mean daily lead contents of the food and feces are plotted as in Figure 3.8, except that the scale is on the right. The peaks during the period of exposure correspond to the periods of maximum ambient temperature during the summer months of the successive years.

The facts indicated in these figures are much the same as those pointed out in connection with Figures 3.10 and 3.11, so that little further discussion is required. It is worthy of note, however, that during the fifth month of the period of exposure, the mean daily concentration of lead in the urine of Subject F.C. was 0.14 mg/liter, and during the fifteenth month, it was 0.16 mg/liter. Neither of these values is necessarily indicative of a dangerous level of lead absorption, but, if maintained consistently for some months, the higher of these two results is potentially dangerous under ordinary conditions of life in the temperate zone. It is important to recognize, therefore, that both of these values, spaced about one year apart, came during the peak of the hot weather in the respective years. They also occurred in association with elevated levels of lead intake in the food. Their unusual character is demonstrated by the fact that the average concentration of lead in the urine, after equilibrium with the exposure had been reached, was approximately 0.085 mg/liter. More than any other portrayal of the data of these two experiments, Figure 3.9 illustrates the difficulty in visualizing the lead metabolism of an individual, as a consistent pattern, on the basis of a few observations of the rate of the urinary excretion of lead.

The data concerning the concentration of lead in the blood are of prime importance in the appraisal of the status of individuals with respect to the relative quantities of lead in their tissues and the significance of such quantities of lead in relation to the hazard. It is necessary to qualify the foregoing statement somewhat. While clearly indicative of the general level of the lead absorption of an individual who is being subjected to exposure to lead, the lead content of the blood is somewhat less representative of the facts when an interval of some months has elapsed since the termination of a mild degree of occupational or other abnormal exposure. Moreover, the lead in the blood is essentially valueless as an indication of the extent of the individual's absorption of certain organic lead compounds, tetraethyllead being the outstanding example.

Figures 3.12 and 3.13 display the average of eight samples of blood collected at weekly intervals (two per week) for each 28-day period in the two experiments. In both figures, each point on the dotted line from left to right represents the average concentration of lead in the blood (obtained using duplicate techniques, dithizone and spectrographic methods) during the respective periods of 28 days throughout the experiment. In Figure 3.12, note the relatively low variability of the concentration of lead in the blood from point to point, and the general trends during the periods before, during, and after the experimental exposure. While Figure 3.13 shows a lack of variability from point to point during all but the period of exposure, note the greater response of Subject F.C. to the higher level of exposure, as compared with Subject M.O.B.

Figure 3.12

Concentration of Lead in the Blood of Subje

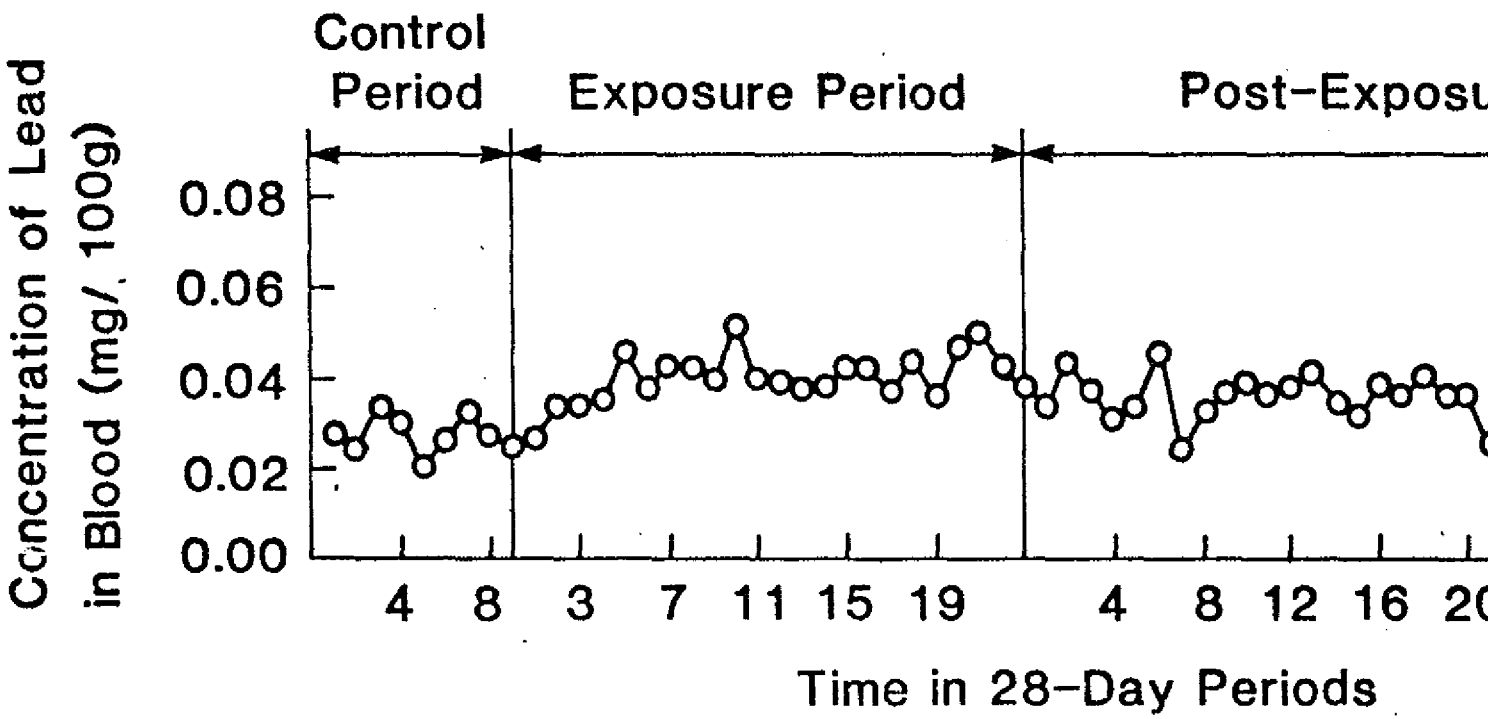
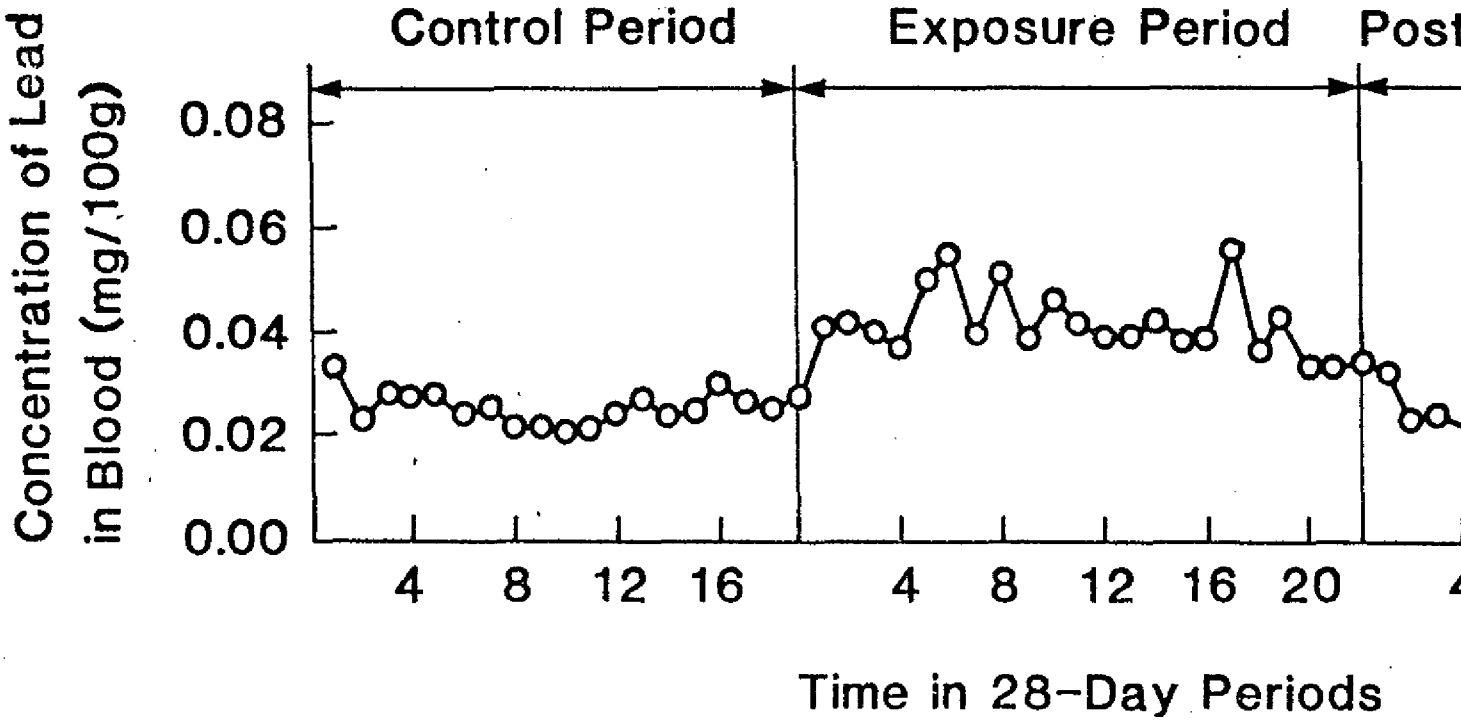


Figure 3.13

Concentration of Lead in the Blood of Subje



Two items are worthy of comment. First, the level of lead concentration in the blood of each subject increased more gradually in response to the experimental exposure and declined more gradually after the termination of the exposure, than did the levels in the urine. Subject M.O.B. reached a stable concentration of lead in his blood at about the seventh month, while Subject F.C. reached a similar state of apparent equilibrium at about the eleventh month. Some of the variability indicated in the blood lead concentration of both subjects may be attributed to analytical deviations, the quantities of lead in these samples being minute. As stated before, two analytical methods were employed in parallel manner and in both cases the analytical error was much too small to influence the general trend of these data or to alter significantly the recorded values, since the unsystematic error is as likely to occur on the high as on the low side.

The average concentration of lead in the blood of Subject M.O.B. at approximate equilibrium was 0.040 mg/100 g, and that of Subject F.C. was 0.045 mg/100 g. Since Subject F.C. started at the average level of 0.025 mg/100 g, and the base level of Subject M.O.B. was higher by approximately 0.003 mg/100 g, the differential is somewhat greater than the average figures at equilibrium indicate. In any case, it is clear that Subject F.C. absorbed more lead than did Subject M.O.B., as was to be expected in accordance with the experimental conditions.

The data obtained during the period after the termination of the exposure, i.e., the excess of the output of lead over the intake in both instances demonstrated that both subjects had accumulated and retained some lead in their bodies during the period of exposure. Calculations made from these data indicate that the total amounts accumulated during

exposure and eliminated in the subsequent period were of the order of 18 to 21 mg in the case of Subject M.O.B. and 25 to 30 mg for Subject F.C. There are good reasons for the belief that the last small residue of the lead that is absorbed during a period of abnormal exposure remains in the body for a long time. It is probable that somewhat more lead was retained by the subjects during their exposures than was eliminated in the extended period of the observations after the exposures had been terminated. This probability, plus the intrinsic, composite, random error of the experimental procedures, makes it necessary to express the retained lead in orders of magnitude rather than in absolute values. Even so, the probable error of the estimates is small, considering the total amounts of lead involved in the experiments, and few assumptions need be made in arriving at the approximate amounts.

For the industrial hygienist, the most significant result of these experiments is the fact that no lead poisoning hazard is associated with the inhalation of air containing a fully respirable and absorbable lead concentration of 0.15 mg/m^3 air over a period of nearly two years. The experiments were carried out under conditions that simulate those of industry except for their strict uniformity and the virtually complete elimination of the ingestion of lead in connection with the day's work. It must be emphasized that the adoption of this level of lead concentration in air as a criterion of absolute safety in industrial employment would make no allowance for longer hours of work and exposure, for diseased states that may interfere with the normal disposition of absorbed lead within the body and its excreta, and, above all, for the situations in lead trades in which the ingestion of lead is a highly significant factor in the composite occupational absorption of lead.

The issue may be raised that the duration of the "occupational" exposure of Subject F.C. was somewhat less than two full years, whereas actual occupational exposure may continue for many years, or, indeed, a lifetime of employment. This point cannot be dismissed lightly, nor can it be disposed of entirely by the experimental evidence, unless one takes the position that no further lead accumulated in the body of either experimental subject after equilibrium with the experimental environment had been reached. Certainly the rate of accumulation, if any, within that period was low, but it cannot be said now with certainty to have been nil. We believe it to have been negligible, because progressive accumulation of lead in the body at a rate as low as 0.04 mg/day (as demonstrated in an experiment on the ingestion of lead) is associated with a significant, progressive increase in the rate of the urinary lead excretion. Because of extensive experience in the medical supervision and clinical monitoring of industrial employees, we are sure that men whose regular rate of urinary lead excretion over a period of many years of stabilized exposure is represented by a concentration of lead of not more than 0.10 mg/liter or by a lead output of not more than 0.12 mg/day are not in danger of developing any form or degree of lead intoxication. Based on this criterion, the margin of safety of the subjects, for an indefinite period of exposure to the prescribed experimental conditions, was large.

INHALATION EXPERIMENT 3
(September 1956 through August 1958)

Protocol

In the first two experiments, it was evident from the identified relationships between ingested lead and the lead in the feces during the subjects' periods of exposure that inhaled lead particles escaped entrapment in the upper respiratory tract. To emphasize this point, a third experiment was initiated in which Subject F.C. was reexposed to airborne lead particles following his first post-exposure period. This 80-week period between the conclusion of the subject's first period of intermittent exposure and the initiation of his second restored him to very nearly his original, normal body burden of lead. At this time, he returned to the respiratory chamber on the same schedule as before. The only variant in the experimental conditions, as compared with those of his first period of exposure, was the size of the particles of lead sesquioxide. These particles ranged up to a maximum of four microns in diameter (90 percent of the particles were smaller than two microns and 50 percent were under 0.9 micron, in diameter) during the second exposure period.

Discussion and Results of Experiment 3

Figures 3.14 and 3.15 demonstrate that the larger lead particles to which Subject F.C. was exposed during the second period were trapped in the upper respiratory tract and excreted in the feces. Figure 3.15 corresponds to Figure 3.14 in every way except that it presents the results of exposure to larger lead particles. The first period ("Period After Termination of Exposure") shown in Figure 3.15 corresponds to the last period shown in Figure 3.14.

Figure 3.14

Comparison of Alimentary Lead Intake a
Lead Output of Subject F.C.

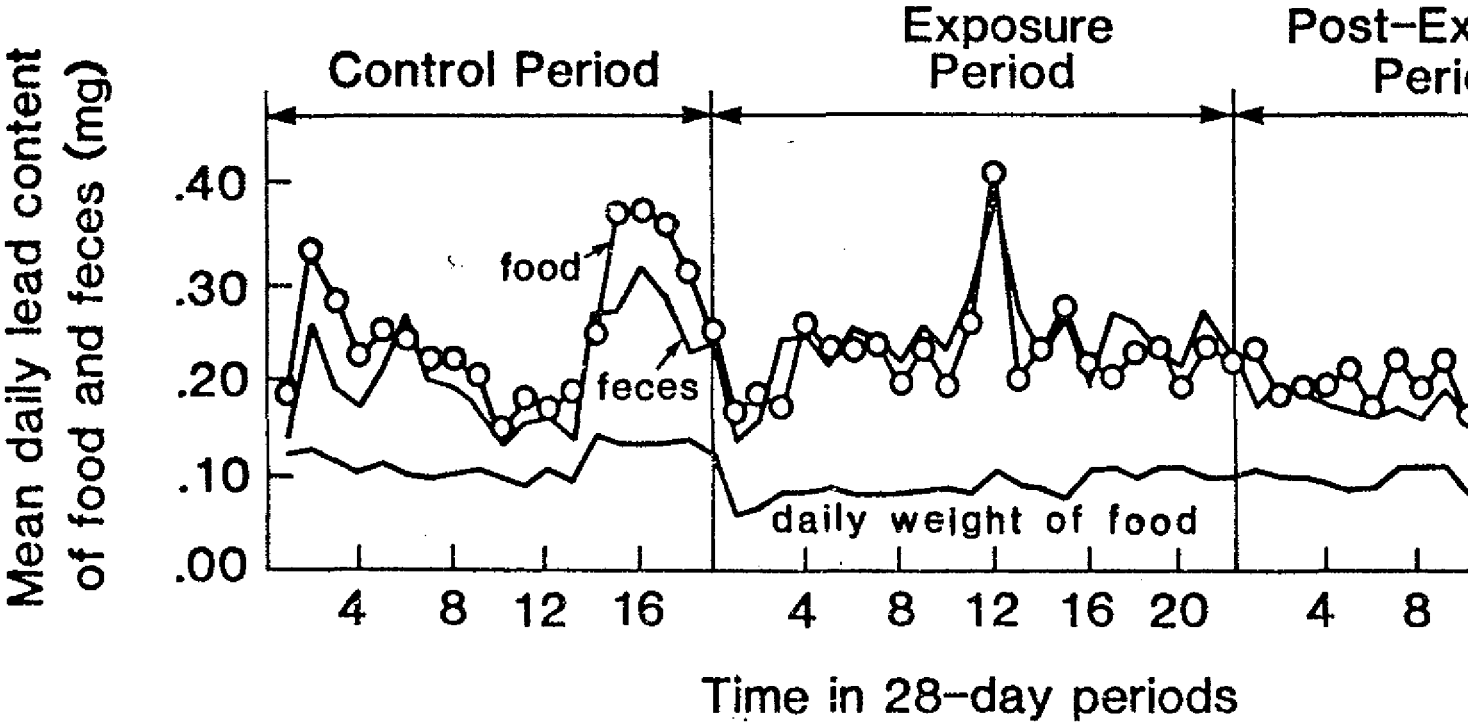
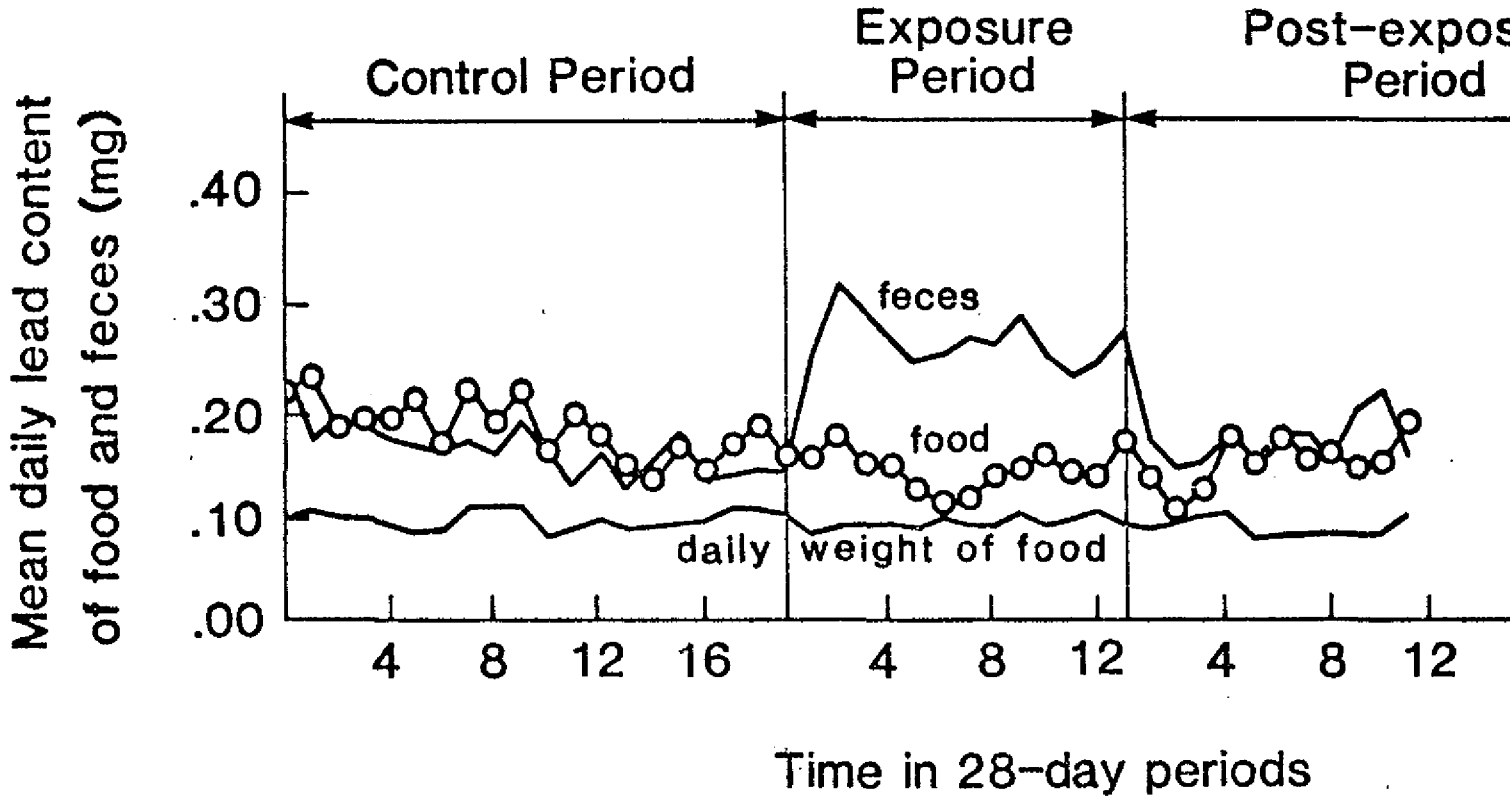


Figure 3.15

Comparison of Alimentary Lead Intake and Lead
of Subject F.C. During His Second Exposure P

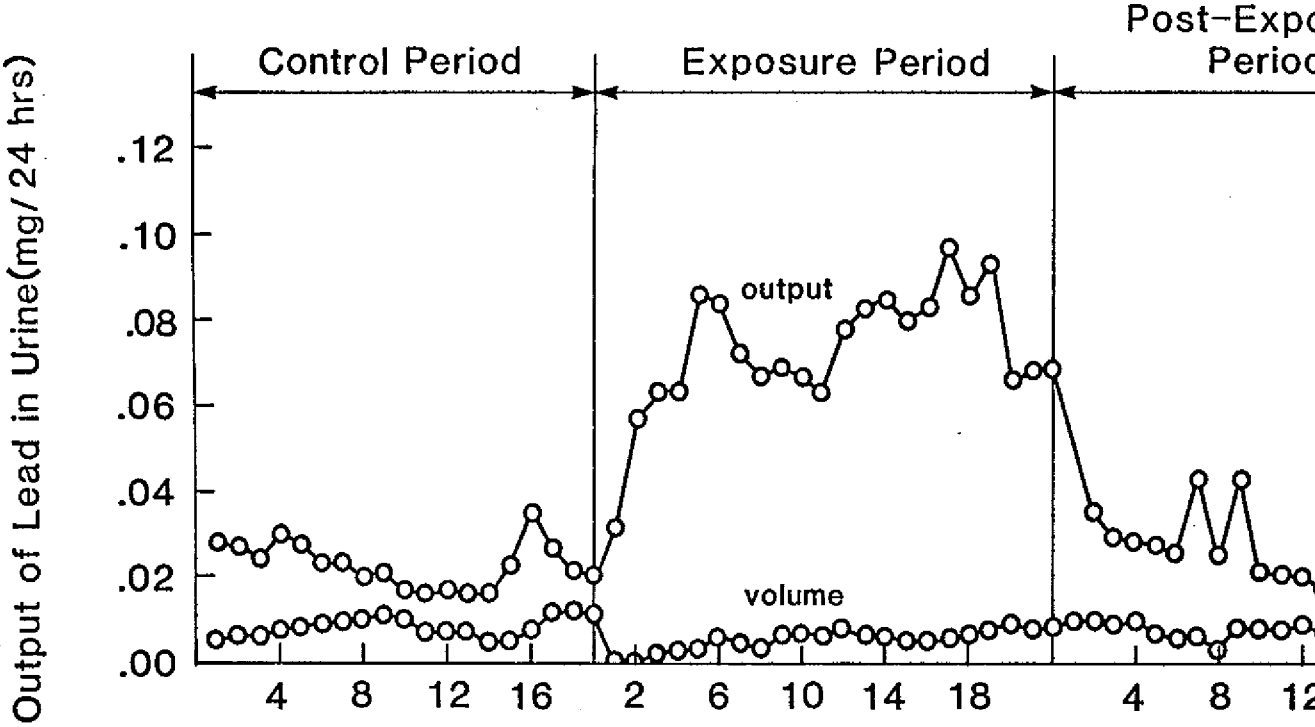


These figures illustrate that the larger lead particles of the second exposure were trapped in the upper respiratory passages, were swallowed, and appeared in the feces, to which they contributed almost as much lead as that which had been ingested in food (see "Period of Exposure" in Figure 3.15). In fact, the particulate lead that reached the subject's alimentary tract from the air of the chamber amounted to about 20 percent of the total quantity that, by calculation, may reasonably be expected to have been taken into his respiratory tract during his period within the chamber. Inasmuch as somewhat more than half (55 percent) of the lead inhaled was found in the exhaled air of the subject under these conditions, it appears that approximately 40 percent of the inhaled lead that separated out of the air in some part of the respiratory tract subsequently found its way into the alimentary tract. Furthermore, according to the results of previous experiments, only 10 to 12 percent of the lead swallowed was absorbed in the alimentary tract, as opposed to the essentially complete absorption of that which was deposited on the membranes of the respiratory tract. Thus, one might suspect that the extent of the absorption of lead under these experimental conditions, as revealed by the excretion of lead in the urine, may have been appreciably less than it had been when the subject had inhaled the more highly dispersed particles.

In Figure 3.16, for each period of 28 days of the entire initial experiment in which Subject F.C. was engaged, the mean urinary output of lead per day is plotted with the mean urinary volume during the corresponding period of time. In the control period, one can see the sharp response to the increased intake of lead in food and beverages, and a little later, the initial and subsequent response to the induced

Figure 3.16

Comparison of Daily Output of Lead in Urine to Daily Volume of Urine of Subject F.C.



respiratory exposure in relation to the finely dispersed lead in the air of the chamber becomes evident. The initial response was prompt, after which it increased for 20 weeks and then diminished. The seasonal factor was not notably involved in this decrease, as the urinary volume, which was at its minimum some three months earlier, discloses. This phenomenon of an apparently excessive response before leveling out has regularly occurred in experiments involving exposure to the highly dispersed lead sesquioxide in the air of the chamber.

Despite the lead output variability in the urine during the exposure period, the trend during that period is unmistakable. A peak in the mean output of lead (0.086 mg per day) was reached after about 24 weeks; this was exceeded on only two subsequent occasions. The average height of the plateau during the period of the respiratory exposure was somewhat above the level of 0.07 mg per day. This level was maintained during the last 12 weeks of the exposure; it was only slightly higher than it had been 68 weeks earlier.

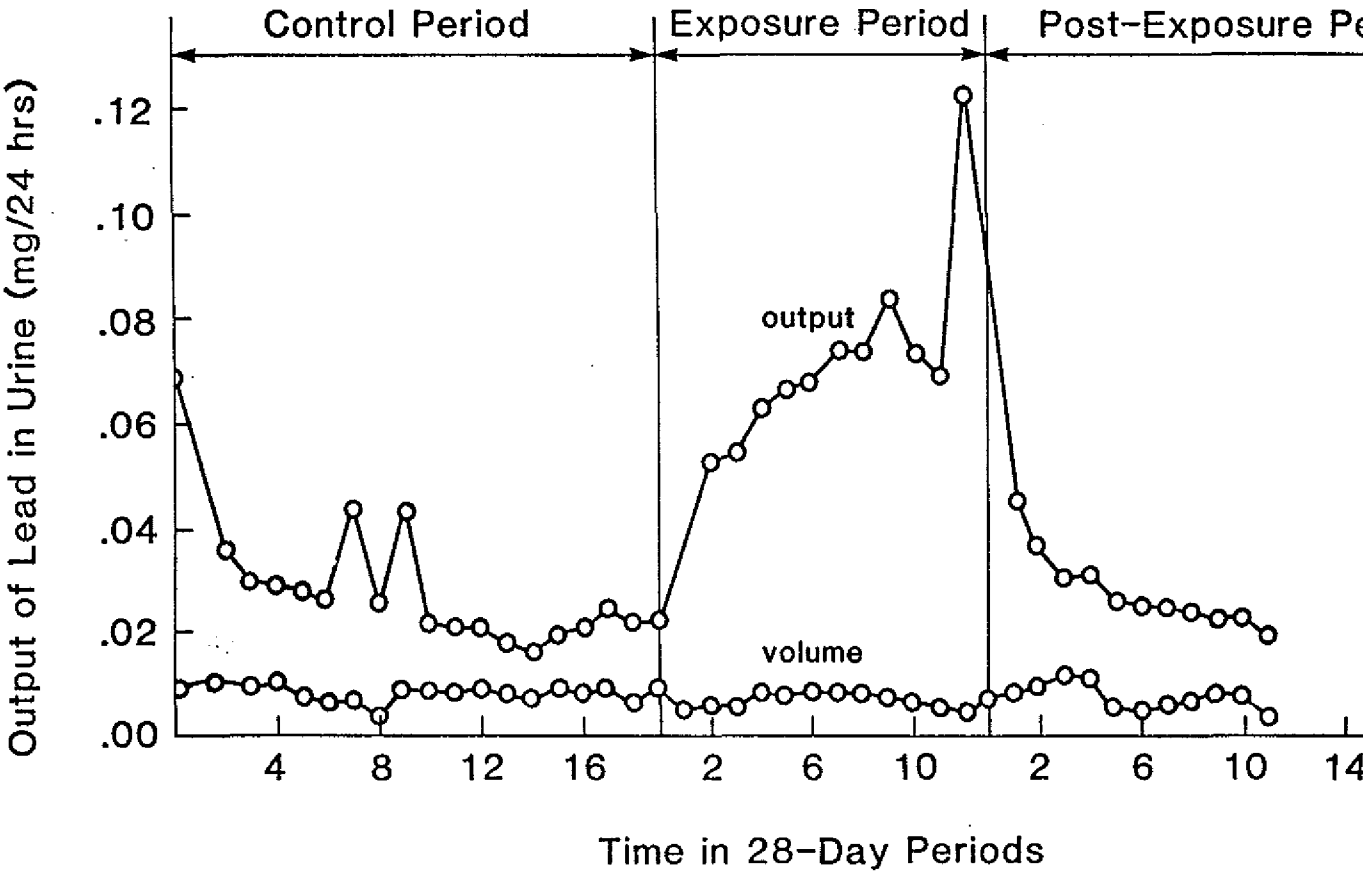
Following the termination of the subject's intermittent occupancy of the respiratory chamber, the output of lead in the urine decreased precipitously. This demonstrated that the previously persistent elevation of the lead output in the urine had been maintained by the repetition of the exposure from day to day and not by the accumulation of slowly absorbable lead within the respiratory tract. The further downward trend of the urinary output of lead (interrupted at two points in the curve by the coincidental occurrence of relatively large quantities of lead in the food, as seen in Figure 3.14) illustrates the decremental decrease of the lead retained in the body of the subject during the period of respiratory exposure.

Digressing again briefly to consider the response of this same Subject F.C. to respiratory exposure to the same quantity of lead in coarser dispersion in the atmosphere of the chamber during his second exposure, it may be seen from Figure 3.17, which is analogous to Figure 3.15 in its temporal relationships, that the subject has reacted somewhat differently than he did during his first intermittent exposure in the respiratory chamber. The rate of lead absorption during the entire second period within the chamber was no less than it had been during the first, as judged by the output of lead in the urine during these two periods. The level increased at about the same rate during the early months of the two periods; it reached a somewhat higher level during most of the intermediate months of the second experiment than it had in the first and it was at a higher level at the end of the 52 weeks of the second period of exposure than it had been at the corresponding time in the first.

These differences are not great, but they are too consistent to be ignored. It is in the pattern of the response to the two sets of conditions, however, that the greatest dissimilarity appears. There is no definitive evidence in Figure 3.17 that the urinary output of lead reached a maximum and then leveled out. One is on somewhat uncertain ground in interpreting this fact, because of specific experimental variables that do not correspond entirely. The second exposure period began some three years later than the first, the two did not coincide in their seasonal relationships (the second began 12 weeks earlier in the year than had the first); and they were not of the same duration (the second was terminated at the end of 52 weeks and the first after 88 weeks). One cannot be sure what would have happened had the second exposure

Figure 3.17

Comparison of Daily Output of Lead in Urine to Daily Volume of Urine of Subject F.C. During His Second Experimental Period



period been extended. Nevertheless, the evidence, as it stands, denies the occurrence of the steady state in the second experiment, and it is logical to suspect that no such state would have been reached later. The reason lies in the fact that most of the lead that was diverted from the respiratory tract to the alimentary tract persisted in the latter throughout the intermittent periods of freedom from further respiratory exposure (16 hours per day on five days of the week, and 64 hours over the weekend).

While he was in the respiratory chamber, approximately 20 percent of the lead in the air inhaled by Subject F.C. entered the alimentary tract. To that extent, this experiment simulated the experiments in which lead was ingested with every meal and was being absorbed from the alimentary tract at an approximately constant rate. Under the latter conditions, the rate of the urinary excretion of lead increased progressively at a nearly constant rate. Under the conditions associated with this second experiment in which Subject F.C. engaged, the quantity of lead swallowed from food and beverages, during and for a time after the day's respiratory exposure, was smaller than it had been in any of the experiments in which lead was ingested (being of the approximate order of 0.1 to 0.15 mg per day). However, because this quantity was available for continuing absorption for a day or more, it may have been sufficient to offset the equilibrium that otherwise probably would have been achieved. The continued presence of lead in the body caused a modest progressive increase in the absorption of lead and in the corresponding rate of its excretion.

Also of interest is the fact that the general level of the absorption of lead by Subject F.C. during the second experiment was as high as it had been during the first. There is no doubt that an appreciable

portion of the inhaled lead during the second experiment was diverted to the alimentary tract, where its absorption would be considerably less complete than that in the respiratory tract. However, another factor associated with the size of the particles operated in the opposite direction. The determinations of the lead in the expired air of the subject under the conditions of the two experiments demonstrated that approximately 64 percent by weight of the inhaled lead was being exhaled when the particles were uniformly small (0.05 micron in diameter), while only 54 percent by weight of the larger particles of the second experiment (2 microns in diameter) were so disposed of. These findings were reinforced by similar findings in subsequent experiments.

INHALATION EXPERIMENTS 4, 5, 6, AND 7
(January 1955 through September 1971)

Protocol

Experiments 4, 5, 6, and 7 were performed to verify the findings of Experiments 2 and 3. The major objectives of these experiments were to determine:

- The effects of dosage (lead concentration in air), and lead particle size,
- the effects of exposure type (intermittent versus constant),
- the respiratory tract lead particle retention,
- the ultimate fate (absorption, retention in the body, and excretion) of the inhaled lead as differentiated from ingested lead, and
- whether the gender of the subject influenced experimental results.

In short, the purpose of the experiments was to determine the balance between the intake and the output of lead and to assess the contributions made to the intake of lead through various avenues and the resultant absorption, retention, and excretion of lead over fairly prolonged periods of time.

All of the experimental variables were the same as those in Experiments 1, 2, and 3 with the exception of particle size. The mean dimensions of the particles during Experiments 4 through 7 ranged from 0.75 micron (90 percent smaller than 1.8 micron) through 0.90 micron (90 percent smaller than 2 microns, maximum 4 microns) to 1.2 microns (90 percent smaller than 6 microns, maximum 9 to 15 microns). Subjects M.O.B., M.B., Ju.S. and P.B. were exposed 7.5 hours per day, 5 days per week within the respiratory chamber.

The overall duration of the three periods (control, exposure, and post-exposure) in the four experiments was such that the characteristics of each subject could be established. The control period ranged in

duration from 20 to 80 weeks, the exposure period from 52 to 112 weeks, and the post-exposure period from 5 to 130 weeks.

In addition to those protocols concerned with developing and maintaining the daily specific environmental conditions within the respiratory chambers, another procedure was carried out regularly. The quantities of lead in the air breathed by each subject and in the expired air were determined at weekly intervals during the exposure period.

Summary and Results of Experiments 1 through 6

The following paragraphs are a summary of the conclusions drawn from the lead inhalation experiments performed on six human subjects over an eleven-year period.

1. During the period of experimental exposure within a respiratory chamber, the retention of lead in the respiratory tract ranged (with considerable variability) from the average value of approximately 35 $\pm$ 2 percent when the mean diameter of the particles was of the order of 0.05 micron, up to approximately 54 percent when the mean diameter of the particles was 0.75 micron, and down again to 43 percent (one subject), 45 percent (one subject), 52 percent and 53 percent (one subject), when the air contained larger proportions of larger particles and the mean diameter was near 1 micron (0.9 to 1.2 microns). These percentages are not to be implicitly relied on because of the comparatively high variability of the many observations made under each set of experimental conditions. They represent approximate orders of magnitude, however, and general trends that are believed to be valid.

2. Aside from the prompt occurrence of increased lead concentration in the urine, the most significant characteristic of the response of the subjects to this intermittent respiratory lead exposure (simulating that of occupational exposure to lead fume in that it persisted for 7.5 hours per day, 5 days per week) was the urinary lead concentration increase over the period of several months to a peak above which it did not subsequently go. After a brief period of subsidence, the urinary lead concentration reached a stable level. This level remained essentially unchanged except for an expected degree of variability throughout the remainder of the period of exposure.

When the concentration of lead sesquioxide in the air of the chamber approximated 0.075 mg/m^3 air, the resulting concentration of lead in the urine at the stabilized level approximated 0.048 mg/liter. In another experiment, the subject was exposed to approximately twice the concentration of lead in the air, and the urinary lead concentration plateau was at the level of 0.071 mg/liter. The concentration of lead in the blood of these two subjects differed little at the peak values, which were approximately 0.04 mg/100 grams of whole blood in both instances. However, the lead concentration in the first subject's blood rose to this peak value from an initial level of 0.025 mg/100 grams, while the second subject's initial blood lead concentration was at the lower level of 0.020 mg/100 grams.

In three of the four later experiments, the concentration of lead in the air was approximately the same as that in the second experiment (0.15 mg/m^3 air). The mean size of the particles

dispersed in the air in each of these experiments was greater than in the first and second experiments, and the concentrations of lead in the urine and blood at their stabilized heights closely approximated those of the second experiment (ranging from 0.067 to 0.074 mg/liter in the urine, and 0.035 to 0.045 mg/100 grams in the blood).

3. As anticipated, no demonstrable portion of the lead in the air was deposited in the upper respiratory tract and diverted therefrom into the alimentary tract when the mean diameter of the particles was in the low range (0.05 micron, 90 percent below 0.17 micron). However, when any significant proportion of the particles was in the range above 1 micron in diameter, the quantity of lead evacuated in the feces was well in excess of that which could be accounted for by the lead content of the food and beverages consumed. Under the latter circumstances, lead derived from the air was being absorbed from both the respiratory and the alimentary tracts. In one of the experiments, the diversion of an appreciable portion of the lead into the alimentary tract (which provides less of an opportunity for absorption than the lungs) resulted in a distinctly reduced overall rate of absorption of lead during the period of the experimental exposure, as compared with that obtained in the other experiments. This effect was counteracted to some extent, however, by the virtually continuous absorption of the portion diverted into the alimentary tract. This resulted in a slight but progressive increase in the levels of lead concentration in the urine and blood of this subject during the period of exposure.

4. No significant difference in lead absorption or retention was noted for the female subject, P.B.

5. Under the conditions of these experiments, the inhaltion of air containing 0.15 mg lead/m^3 air posed no hazard to health. While in the exposure chamber the respiratory volumes of the subjects varied somewhat, but these volumes were in the low range since none of the subjects was engaged in activities that greatly augmented respiratory ventilation other than those of the average adult engaged in simple office work. The highest concentration in the blood of any subject was measured following respiratory exposure, for 37.5 hours per week over the period of 102 weeks, to air containing 0.15 mg lead/m^3 air. This peak concentration was 0.045 mg/100 grams (0.074 mg/liter in the urine). Thus in a situation in which the absorption of lead was limited strictly to that derived from the respiratory tract, the margin of safety represented by these findings is obviously more than adequate.

Special attention is called to the significance of the foregoing observations. It was evident from the results of the lead ingestion experiments that the absorption of lead was essentially continuous. This continuous absorption brought about a virtually steady and progressive increase in the output and concentration of lead in the urine and an increase in the concentration of lead in the blood. The effect of this continuous absorption in bringing about a progressive increase in the body burden of lead carries its own implications with respect to the potential hazard associated with any form of continuous exposure to,and absorption of,lead. In contrast, with occupational exposure to airborne

particles of lead compounds of fairly uniform size well below the range of 1 micron in diameter, the intermittent respiratory exposure and absorption brings about a balance between the intake and output of lead. The balance is related to the periods of exposure, when input is high and output is low (relatively), and the periods of nonexposure, when the reverse is true. At the point where these opposed trends neutralize each other an excretory plateau representative of the relative severity of the exposure is established, and this is only as the conditions of exposure are altered. However, when a significant proportion of the lead in the air is diverted into the alimentary tract, freedom from exposure and absorption is lacking during the interval of respiratory nonexposure. The steady state between intake and output is not achieved. This may be a highly important contributing factor to the hazards of occupational exposure to lead, especially during prolonged employment in a dusty environment in which the alimentary absorption of lead is a significant part of the total absorption.

INHALATION EXPERIMENTS 8, 9, AND 10
(February 1959 through September 1963)

Protocol

These experiments were designed to demonstrate the influence of exposure period continuity on the effects of lead exposure in human subjects. The rationale for these experiments developed from the following previously observed facts. When experimental subjects were subjected to the daily oral administration of a standard dosage of lead along with their meals over periods of months and years, a slightly variable but continuous rate of absorption from the alimentary tract, the rate of the excretion of lead in the urine and feces, and the rate of accumulation of lead in the body, with some seasonal (and other) variability, continued at a substantially uniform yearly rate. The accumulation rate gave no sign of tapering off during the entire period of administration of lead, which, in one instance, was 4.5 years. However, when other experimental subjects inhaled lead particles dispersed in air for 7.5 hours per day, 5 days per week (simulating an occupational exposure) under the standardized conditions of a respiratory chamber, the accumulation rate did taper off. In about 16 weeks, the rate of urinary lead excretion and the concentration of lead in the blood increased steadily to a nearly constant level, after which it continued essentially unchanged as long as the experimental conditions remained constant.

By establishing a response gradient of human subjects to incremental increases in the duration of constant lead exposure, the metabolic effects of the exposure could be approximated. To establish this gradient, after their control periods, two subjects, L.D. and Jo.S. were exposed to 0.15 mg lead/m^3 air for periods of time on the following schedule: first for 3 hours per day on every other day, for 16 weeks; then for 6 hours

per day, on every other day, for 16 weeks; then for 9 hours per day, on every other day, for 16 weeks; and finally, for 12 hours per day, on every other day, for 16 weeks. Subject S.B. was exposed to the same airborne lead concentration for periods of 4, 8, and 10 hours per day during his weeks in the chamber. These schedules did not carry the exposure beyond the level that had been established by both occupational experience and physiological experimentation as being well within the limits of safety.

Discussion and Results of Experiments 8, 9, and 10

During each successive period of 16 weeks, as had been the case in every other experiment involving simulated occupational exposure to lead (i.e., 37.5 hours per week), the level of the urinary output of lead per day, the concentration of lead in the urine of the subjects, and the concentration of lead in their blood rose to a certain point and then continued at essentially constant levels, as long as the conditions of exposure remained unchanged. Each incremental increase in the weekly duration of the exposure resulted in a further graduated increase in the levels of lead in the urine and blood; a line connecting the points representing the final levels (or the leveled-out plateaus) of the concentration of lead in the blood that had been reached in the successive periods of 16 weeks became a straight line with a uniform upward slope. The results of the extension of this line at the same slope to a point that corresponded, in the case of each subject, to continuous exposure (i.e, 168 hours per week) is shown in Figure 3.18 (Subject L.D.), in Figure 3.19 (Subject S.B.), and in Figure 3.20 (Subject Jo.S.). Other analytical data for these three subjects have been grouped and are charted in Figures 3.21 and 3.22 (Subject L.D.), in Figures 3.23 and 3.24 (Subject S.B.), and in Figures 3.25 and 3.26 (Subject Jo.S.).

The general features of these charts are similar to those observed in previous experiments, the results of which are discussed elsewhere. It may be useful, however, to call attention to certain characteristics. First and foremost is the similarity of two of the sets of charts. We have learned to expect that the behavior of human subjects will be much the same under the same experimental conditions, but it is nonetheless impressive to note that two of the individuals have reacted similarly. In the Laboratory their environments were as nearly identical as they could be made, while differing elsewhere according to the customs of two different households and the habits of life of each individual, one of whom (L.D., Figure 3.18), a craftsman, was married and "settled down", and the other (Jo.S., Figure 3.20) was a night school student who was unmarried and was planning a technical career. The concentration of lead in the blood of Subject L.D. at the start of the experiment was slightly lower than that of Subject Jo.S. during the initial (control) period (0.022* versus 0.024* mg/100 g), still slightly lower by about the same margin at the end of the total period of experimental exposure, and, as the result of the extrapolation, still indicating the same relationship, with the slope of the plotted curves being remarkably similar. It is instructive to compare the end results of the intermittent respiratory exposure to air containing 150 mg of lead with those that emerge from the extrapolative process as an expression of <u>continuous</u> respiratory exposure. The concentration

*These differences are negligible in the practical sense. They are remarked on only because they have resulted from calculations of data that were limited to the second decimal.

Figure 3.18

Extrapolation of Blood Lead Levels to 64 Mo

Lead Inhalation Exposure (Subject L.D.)

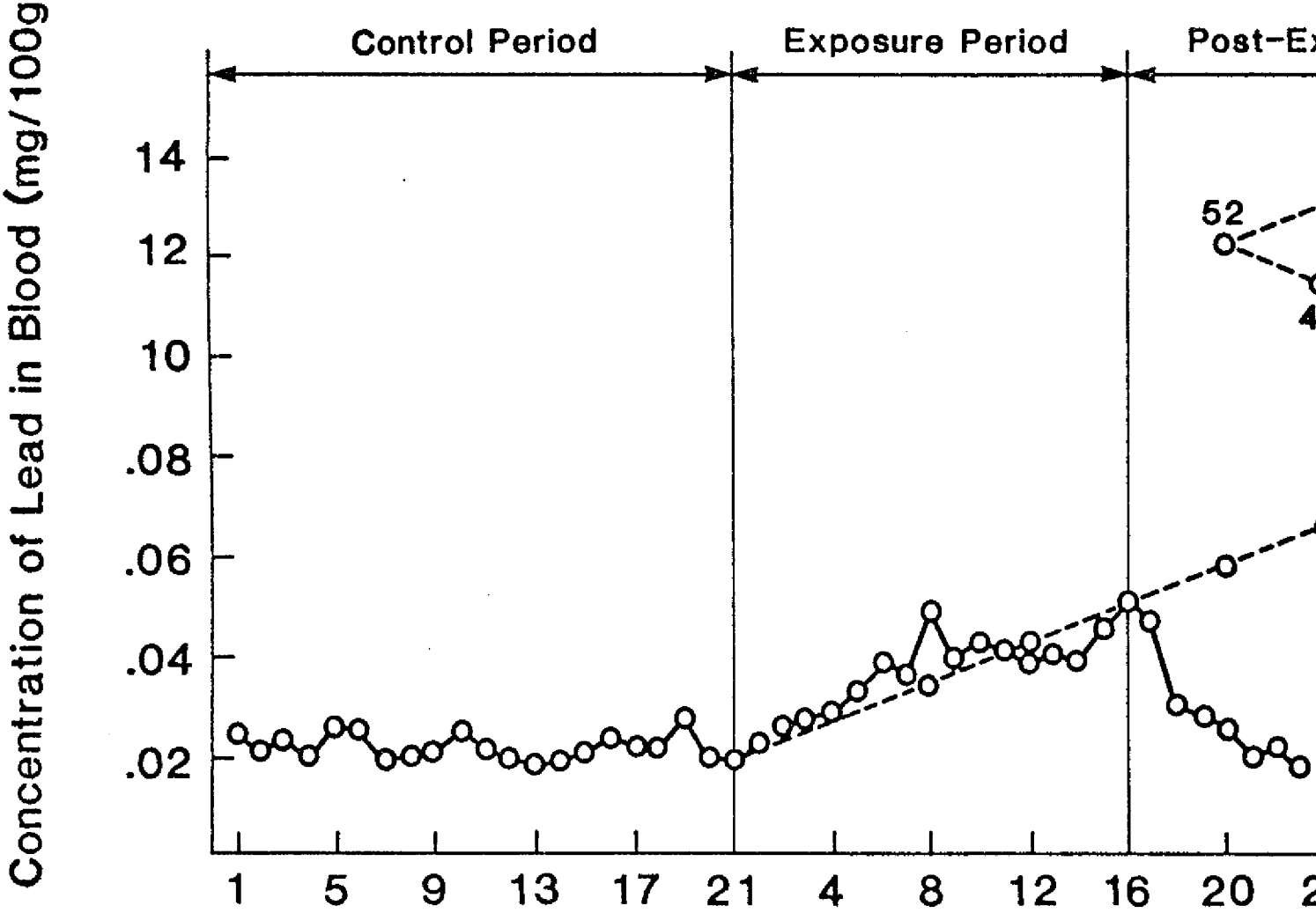


Figure 3.19

Extrapolation of Blood Lead Levels to 64 Month
Lead Inhalation Exposure (Subject S.B.)

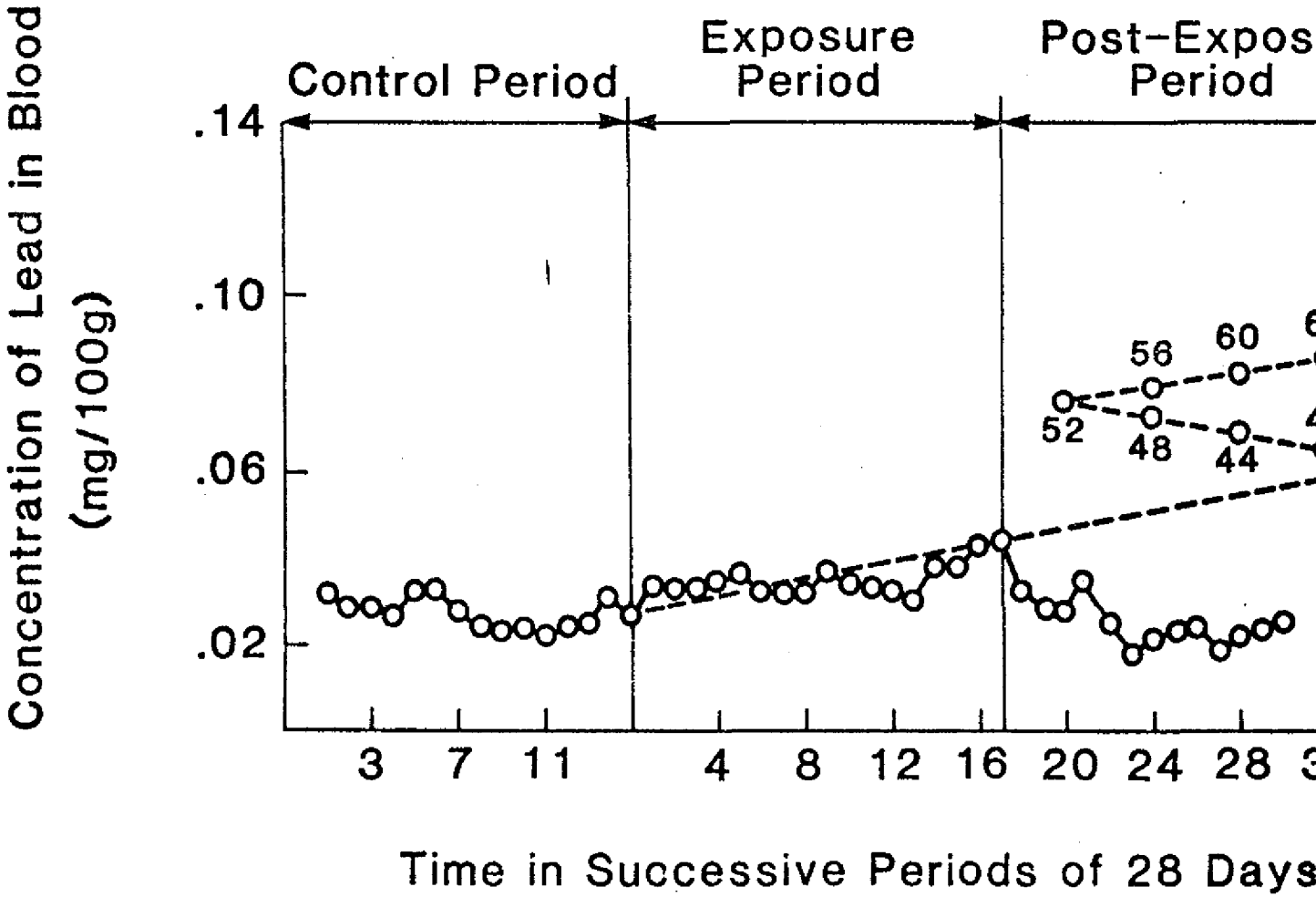
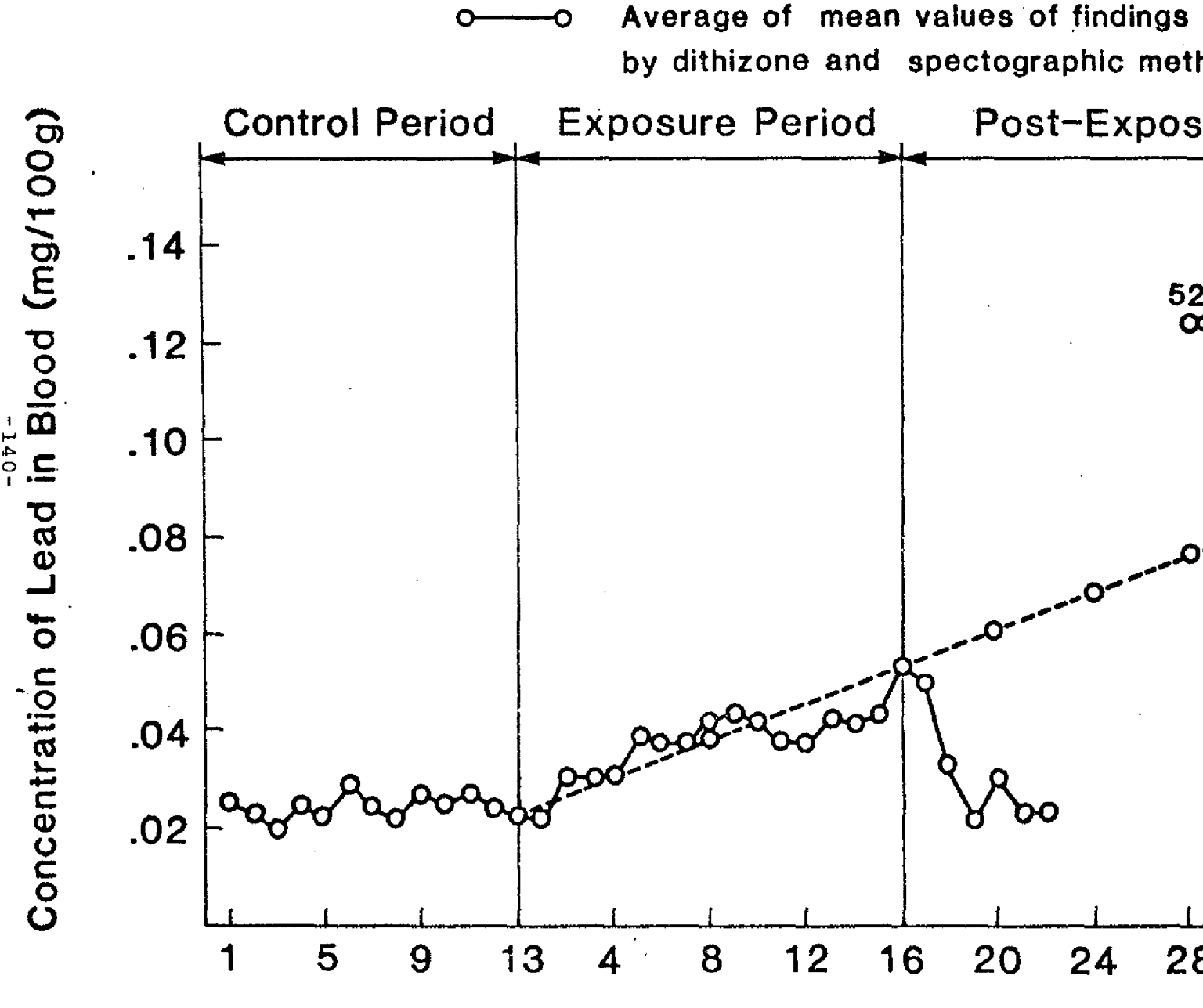


Figure 3.20

Extrapolation of Blood Lead Levels to 64 Mo
of Lead Inhalation Exposure (Subject Jo.S.)



Observed relationship between alimentary lead intake and fecal lead output of Subject L.D.

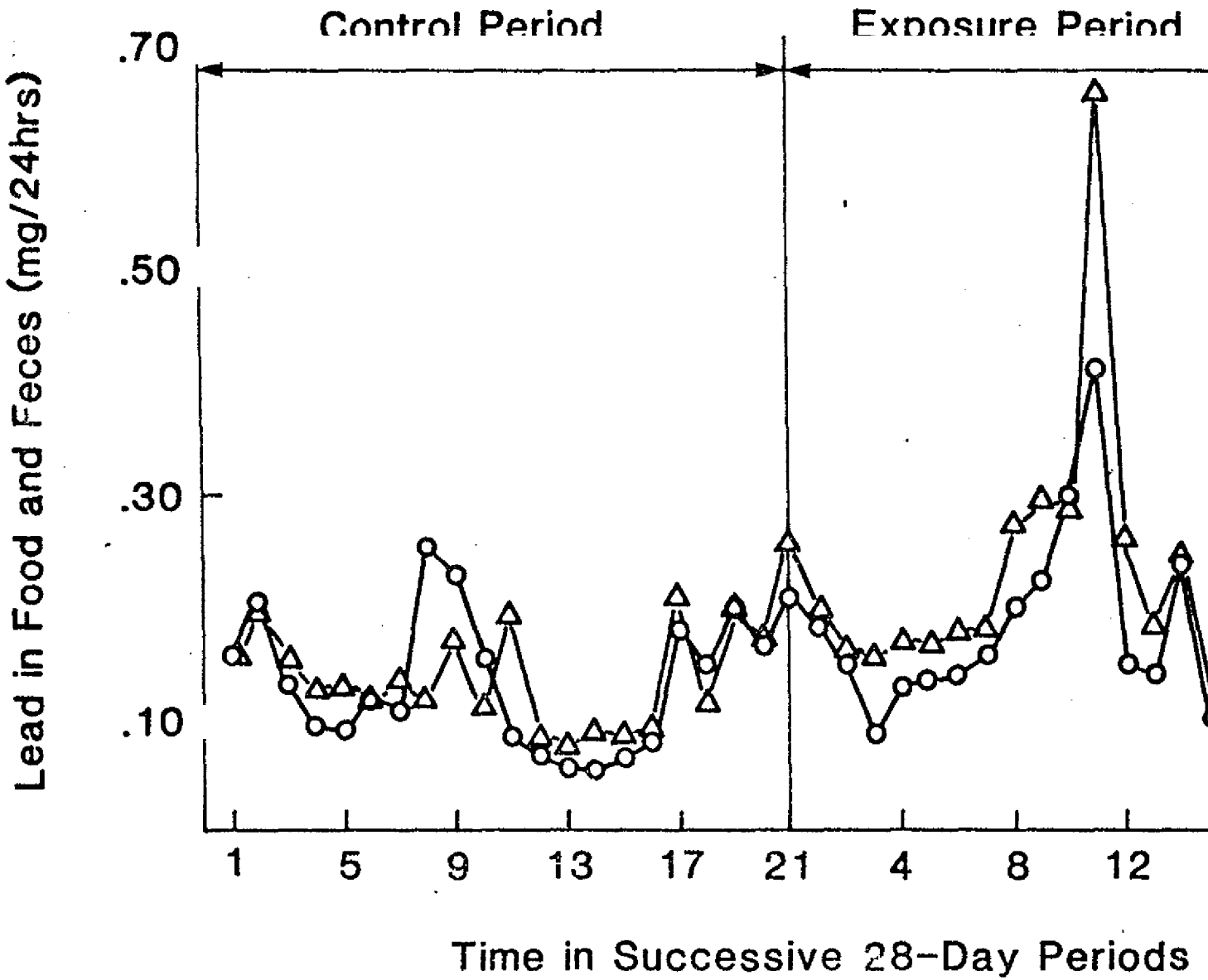


Figure 3.22

Mean Daily Output of Lead In in Urine (Subjec

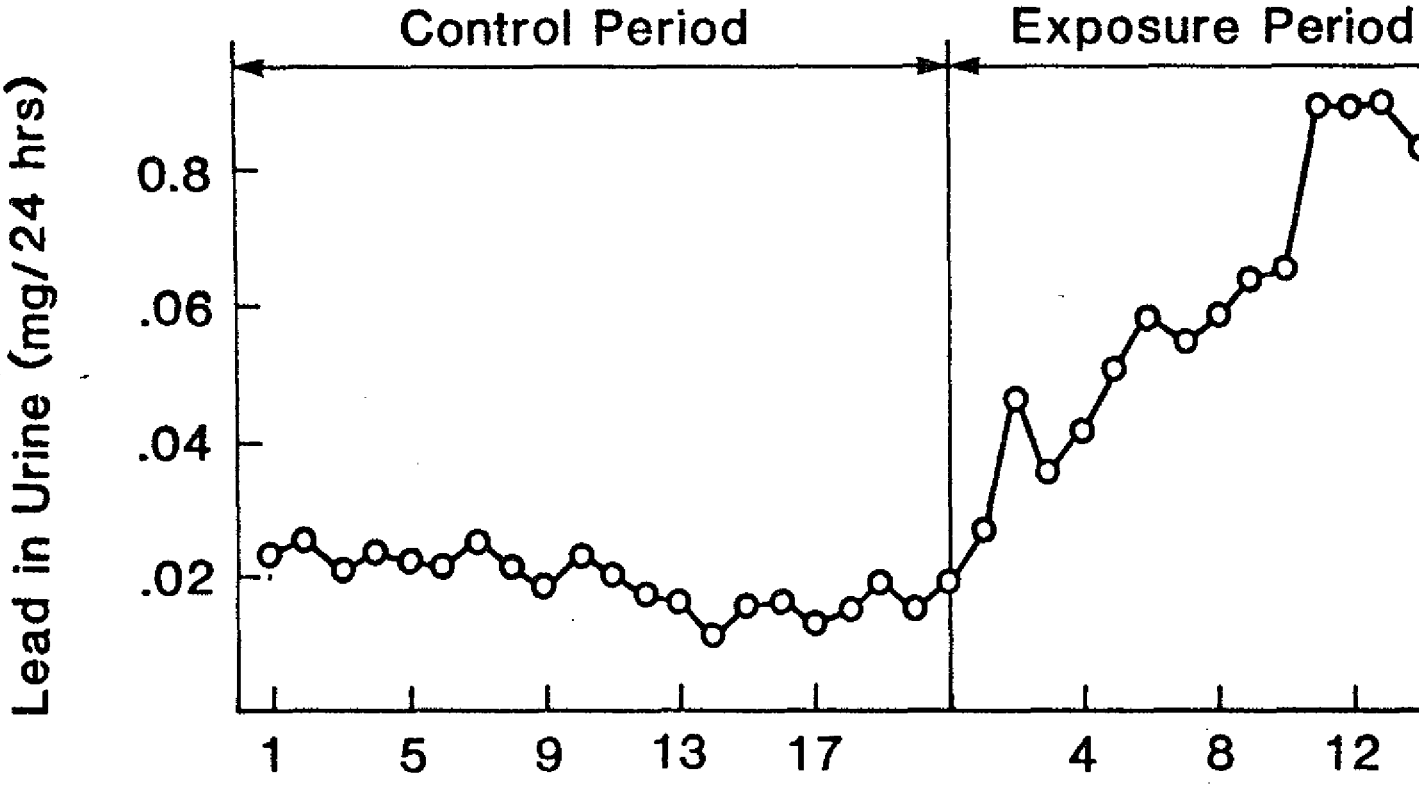


Figure 3.23

Observed Relationship Between Alimentary Lead and Fecal Lead Output in Subject S.B.

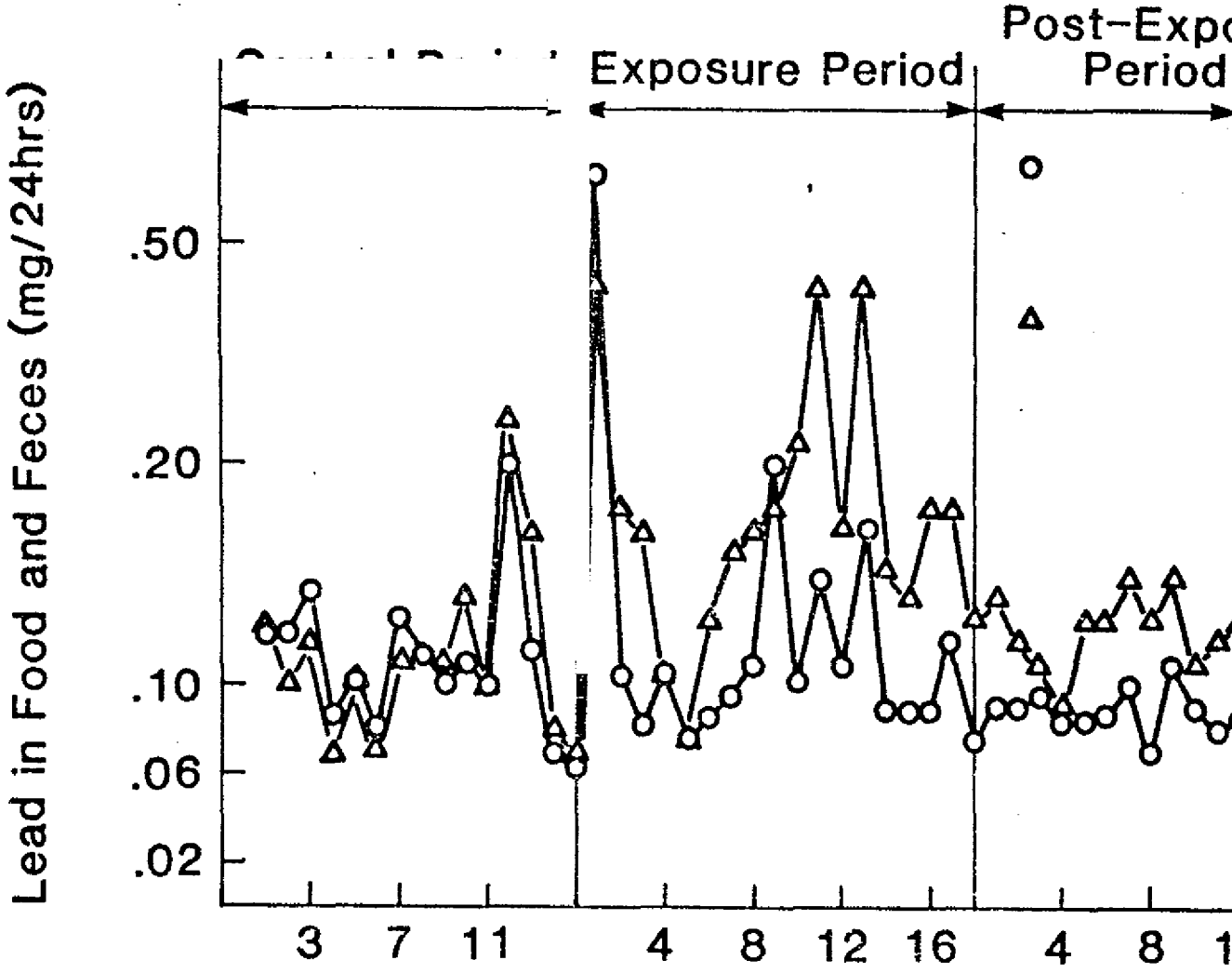


Figure 3.24

Mean Daily Output of Lead in Urine (Subject S

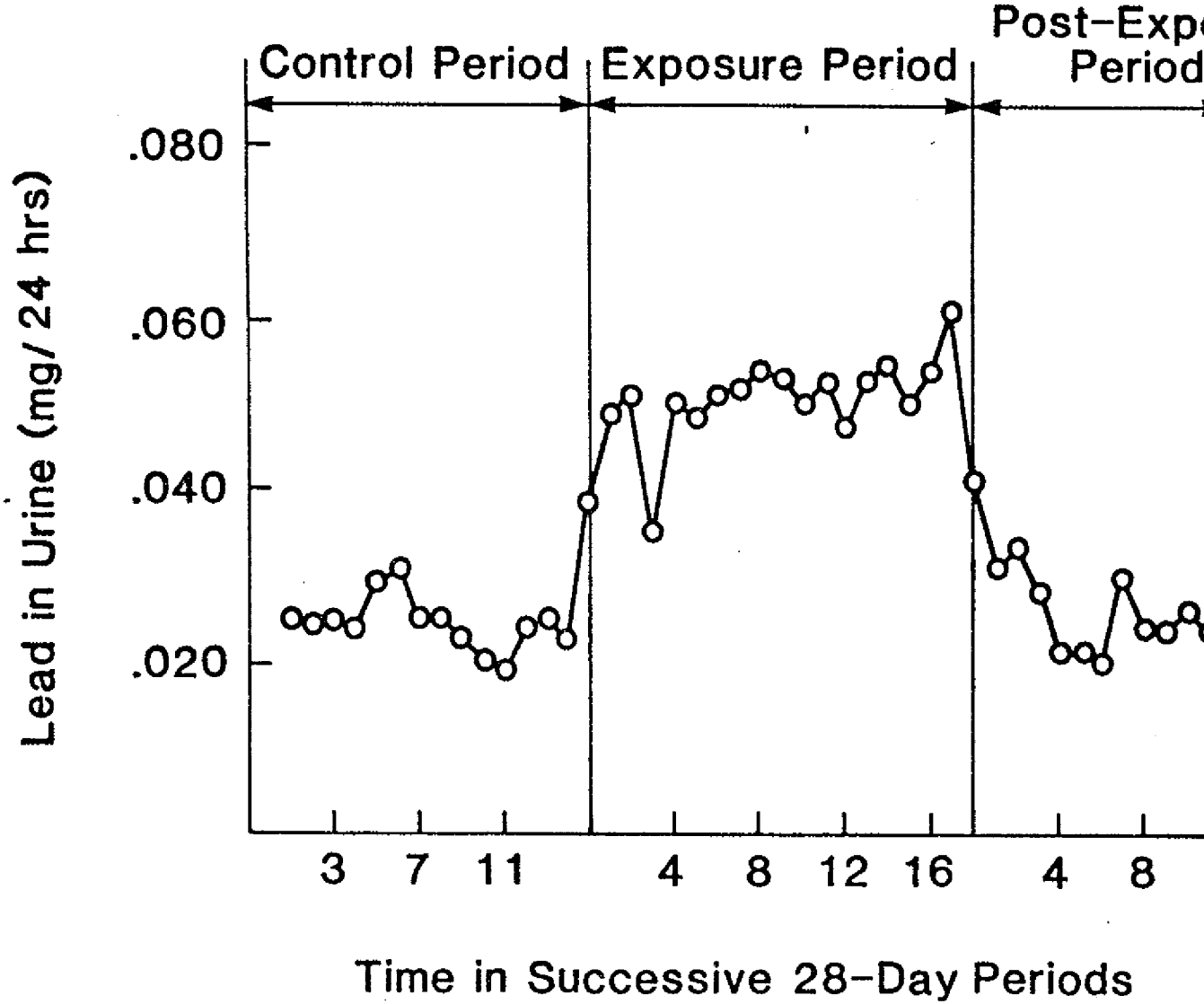
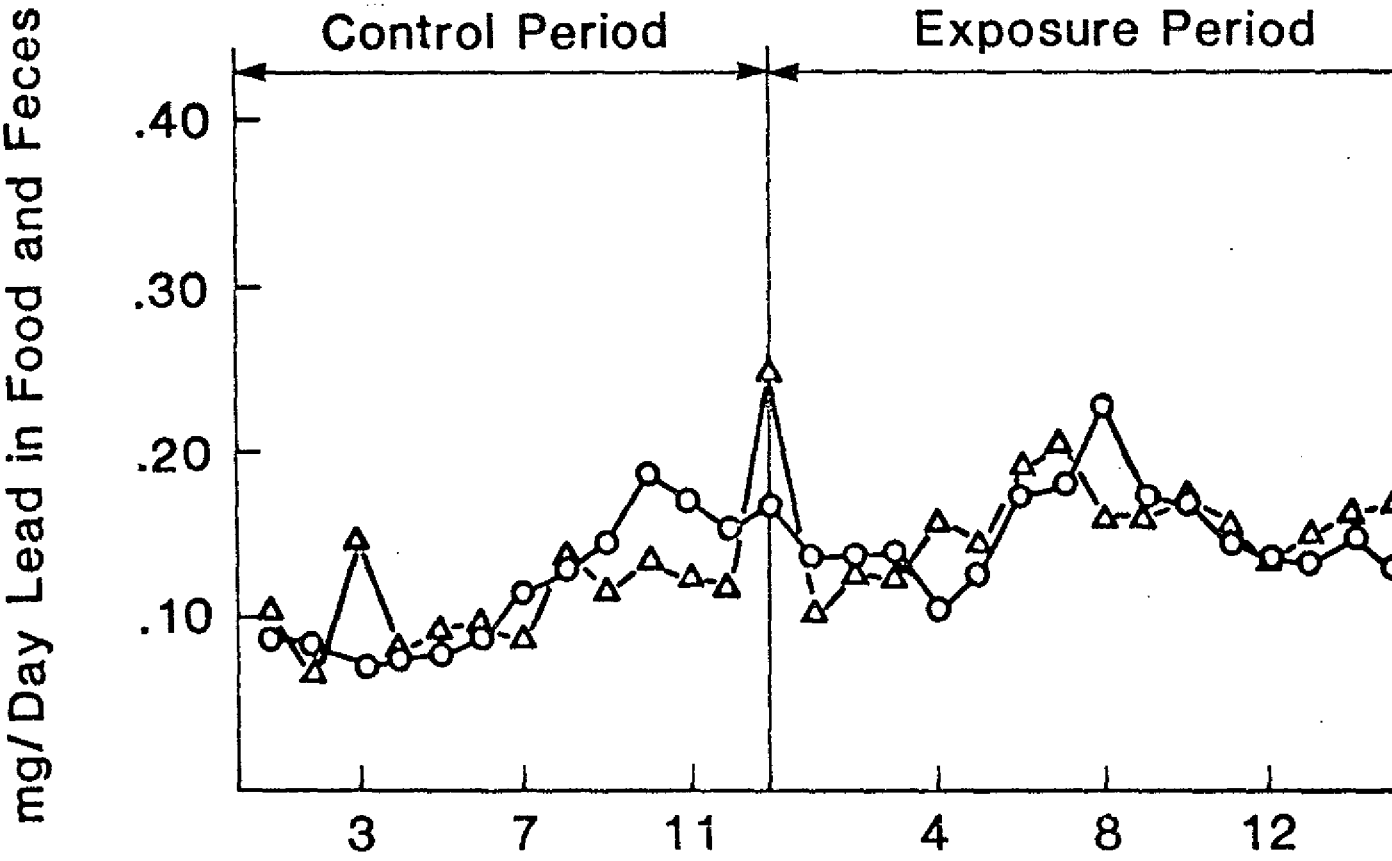


Figure 3.25

Observed Relationship Between Alimentary
and and Fecal Lead Output of Subject

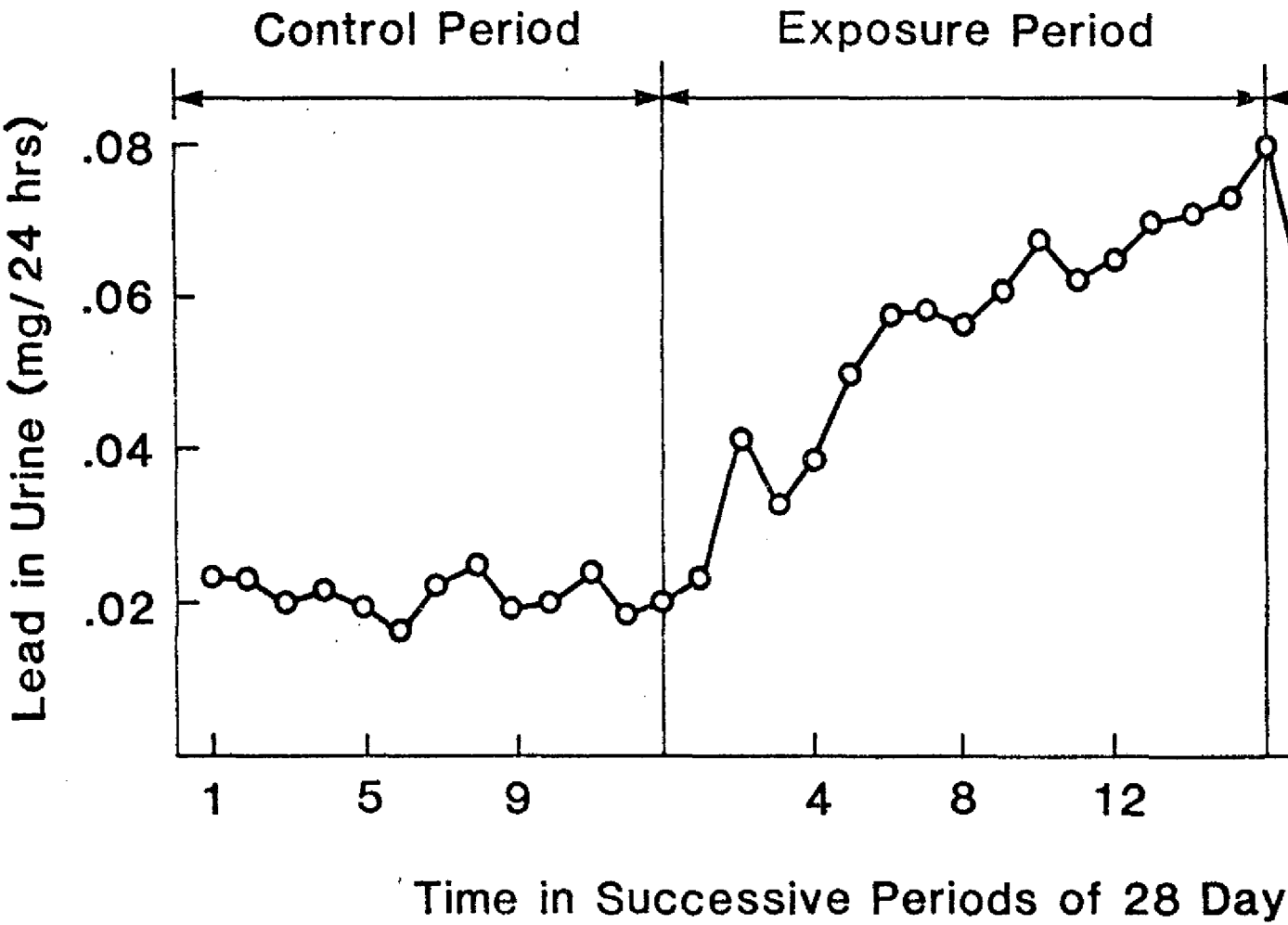


○ Mean daily intake of lead in food
△ Mean daily output of lead in feces

Figure 3.26

Mean Daily Output of Lead in Urine (Subject

Po



of lead in the blood was 0.045* and 0.053* mg/100 g for Subjects L.D. and Jo.S., respectively, after 16 weeks of exposure for 42 hours per week (comparable roughly to the industrial week). Their blood lead concentrations reached the derived levels of 0.145* and 0.148*, respectively, at some point in time (certainly less than three years), after the continuous inhalation of air containing the same concentration of lead.

The evidence furnished by observations of the health effects of occupational exposure to a sustained lead concentration in the industrial atmosphere justifies the conclusion that the concentration of lead in the blood of workmen increases for a time, until it reaches a level that undergoes little or no further increase over the period of many years. In our experience, under conditions in which the concentration in the blood of every workman remains below 0.08 mg/100 g (i.e., in view of the analytical deviation of $\pm$ 0.01, not in excess of 0.07 mg/100 g), no case of lead poisoning will occur. On the other hand, the concentration of approximately 0.15 mg lead/100 g blood is unduly high. While it does not follow that every individual whose blood contains such a concentration of lead has or will have lead poisoning, some become ill promptly and others later, while some, unaccountably, remain well.

It is reasonable to conclude from the results of these experiments that had the exposure been continuous (i.e., all day every day) at the 0.15 mg lead/m^3 air, the concentration of lead in the blood would

*These differences are negligible in the practical sense. They are remarked on only because they have resulted from calculations of data that were limited to the second decimal.

have reached the level of approximately 0.16 mg/100 g in somewhat less than two years of exposure. It has been clearly demonstrated that the respiratory exposure of normal men to highly dispersed lead sesquioxide in the atmosphere on a schedule that is comparable to that of industrial employment (approximately 40 hours per week) will not result in a dangerous degree of absorption. The influence of discontinuity of exposure to lead, in contrast to that of continuity, may thus be appreciated on a fairly quantitative basis.

The results of these experiments achieve their greatest practical importance for present purposes in indicating the feasibility of this method of investigation for determining the maximum concentration of lead in the ambient atmosphere (in association with the current intake of lead in food and beverages) that is compatible with human health and well-being. The promptness and the quantitative orderliness of the physiological response to a graduated shift toward continuity of exposure, as represented best by the incremental increase in the concentration of lead in the blood, demonstrates clearly the essential reliability of this criterion as an indicator of the absorption of lead, and gives strong support to the experimental hypothesis that was being tested.

INHALATION EXPERIMENTS 11 AND 12
(March 1963 through October 1966)

Protocol

Having demonstrated the influence of time (i.e., the continuity of the period of exposure) in Experiments 8, 9, and 10, the next experimental step involved the determination of the highest concentration of lead in the air to which a normal individual might be subjected continuously without incurring a measurable increase in the lead concentration in his urine and blood, presumably, without significant increase in the "body burden" of lead. For practical purposes, this might be regarded as the intensity of continuous respiratory exposure that would just barely result in a statistically demonstrable increase in the urinary output (or concentration) of lead without a demonstrable increase in the concentration of lead in the blood. Prior experimental evidence has shown that such a situation results from a careful adjustment of the increment of lead added experimentally every day to the quantity absorbed from day to day under normal conditions.

In essentially parallel experiments, Subjects N.K. and S.S. were subjected to exposure to lead sesquioxide particles ranging from 0.01 to 0.18 micron in diameter (mean diameter, 0.05 micron) dispersed in the air of the two respiratory chambers in the concentration of approximately 0.01 mg lead/m^3 air. After preliminary control observations over a period of months, each of these subjects was introduced into a chamber for three hours on every other day (10.5 hours per week) over a period of 12 weeks. Subsequently the duration of the exposure per day was doubled, tripled, and further multiplied until one of the subjects (N.K.) was spending 73.5 hours per week in the chamber while the other (S.S), who started

later, was spending 52.5 hours per week in the chamber. Thus both subjects had had 16-week exposure periods of 10.5, 21, 31.5,and 42 hours per week.

Discussion and Results of Experiments 11 and 12

During all but the latter exposure periods when Subjects N.K. and S.S. spent the greatest number of hours per week in the chambers, neither subject demonstrated any evident excretory response to the experimental regimen. The quantity of lead absorbed daily in the lungs of these subjects had not been sufficient under the exposure conditions to be demonstrated when compared to the variability of the daily urinary excretion of lead induced by the absorption from the alimentary tract. To be more specific, the quantities of lead absorbed from the alimentary tract from day to day were so much larger (and more variable) than the quantities absorbed daily from the lung that the latter could not be detected.

In the latter part of the exposure periods, there was a slight increase in the output of lead in the urine and also, somewhat surprisingly in view of the scantiness of the elevation of the urinary excretion, a slight increase in the concentration of lead in the blood of both subjects. The increase was irregular, late in the case of Subject S.S., and of such slight proportions in both instances as to be of dubious significance. However, the trends appear to be sufficiently persistent to be valid. Unfortunately, their interpretation is uncertain because the lead content of the food and feces of both subjects was somewhat more variable* than usual, and the increases above the average level tended to coincide with those of the output of lead in the urine and the concentration of lead

*The gross contamination of the food of Subject N.K. resulted from his consumption of the flesh of a steer killed by gunshot which had shattered and spread minute fragments of the bullet beyond visible pathways.

in the blood. In neither case was it possible to plot a curve that would adequately fit the findings in either urine or blood and from which a valid extrapolation could be projected. (In Figure 3.27, the upward and downward trends in the concentration of lead in the blood of Subject S.S. for several months at a time have been indicated roughly by a dotted line joined with squares.) It may be that the concentration of 0.010 mg lead/m^3 air is near the threshold value that is being sought in these experiments. To ascribe such significance to these findings would be to deal irresponsibly with evidence of a type that has previously been found to be misleading. In the hope of clarifying these results, Experiments 13, 14, and 15 were carried out. These experiments are discussed in the next section.

INHALATION EXPERIMENTS 13, 14, AND 15
(May 1966 through December 1969)

Subject S.S., of the experiment described previously, agreed to participate in a second experiment after a post-exposure period of further observations intended to reveal any decrease in response following the termination of his former experimental exposure. He and a new subject (H.R.) began a regimen of exposure to airborne lead sesquioxide at an experimental lead concentration of 0.02 mg lead/m^3 air, double the airborne concentration used in Experiments 11 and 12. The lead particle size was the same as that used in Experiments 11 and 12 (mean diameter 0.05 micron, with a maximum of 0.18 micron). The initial proportion of the time spent by each subject within his chamber was 21 hours of the 168 hours of a full week; the exposure was continued for 20 weeks. The further schedule involved corresponding periods of time (20 or 16 weeks, either of which appeared to be sufficient to elicit the maximum excretory response), in succession, at rates of 31.5, 42.0, 52.5, 63.0, and 73.5 hours per week.

Subject H.R. found another job and, with approval, discontinued his services in August 1967. Because of advanced notice that this would occur, the course of the experiment was modified somewhat to gain as much information as might be possible in the short time available. The experiment was repeated using another man, Subject D.H. He was brought into the experiment promptly after he was examined and found to be acceptable. After a preliminary period of 24 weeks which were sufficient to cover the two most different seasons of the year, he began his experimental schedule when Subject H.R.'s exposure had ended.

Subject S.S. completed the described experiment on schedule.

Discussion and Results of Experiments 13, 14, and 15

After approximately eight months in the respiratory chamber, it appeared that Subject S.S. was responding to the lead exposure by excreting a somewhat larger quantity of lead in his urine than he had previously. This trend continued throughout the remainder of the experimental exposure. By careful inspection of the plotted data of lead in urine and blood shown in Figures 3.27 and 3.28, certain crude facts are evident.

There was a regular increase in the rate of the excretion of lead in the urine, following an initial significant increase at about the middle of the period during which the exposure was maintained for 42 hours out of the 168 hours of the week. Subject S.S. did not yield any demonstrable increase in his urinary excretion of lead during the 20 weeks of his exposure for 21 hours per week (12.5 percent of the time) to 0.02 mg lead/m^3 respired air. There is dubious evidence of some increase (too slight to be beyond the range of ordinary variability) during the latter half of the period of 16 weeks of exposure for 31.5 hours per week. The trend seems unmistakable from there on to the end of the experiment, despite certain irregularities in the rate of the increase from one period to the next. Seasonal effects have been observed in all of our experiments in which the magnitude of the exposure to lead has remained nearly constant throughout a year or more, and despite the primary trend, these have to be taken into account when drawing conclusions.

The straight line drawn in Figure 3.28 represents the approximate slope of the incremental increase in the urinary excretion of lead. This line has been projected to the point that, hypothetically, it is an

Figure 3.27

Quantities of Lead Measured in Subject S.S.'s Blood, Urine, and Alimentary Intake

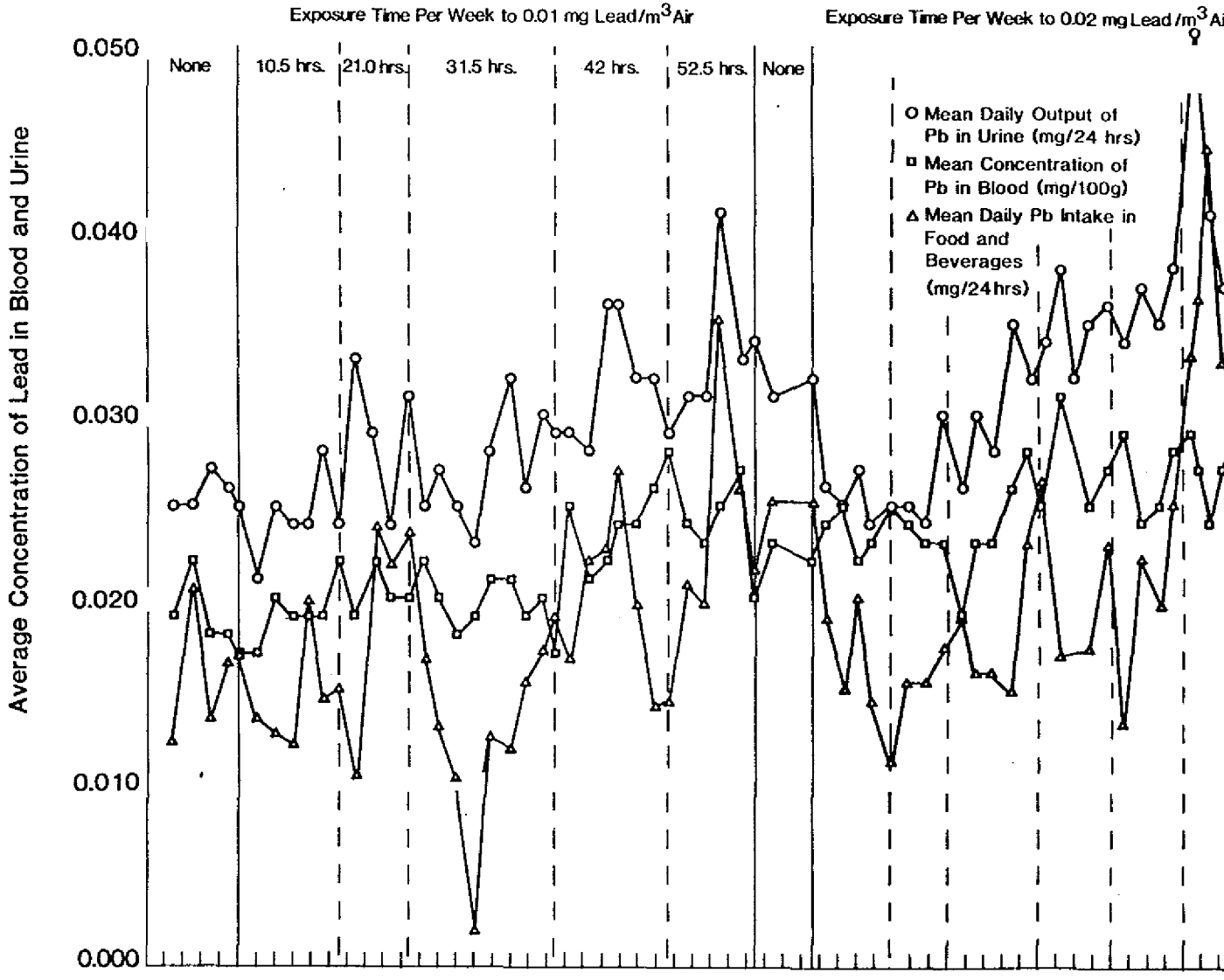
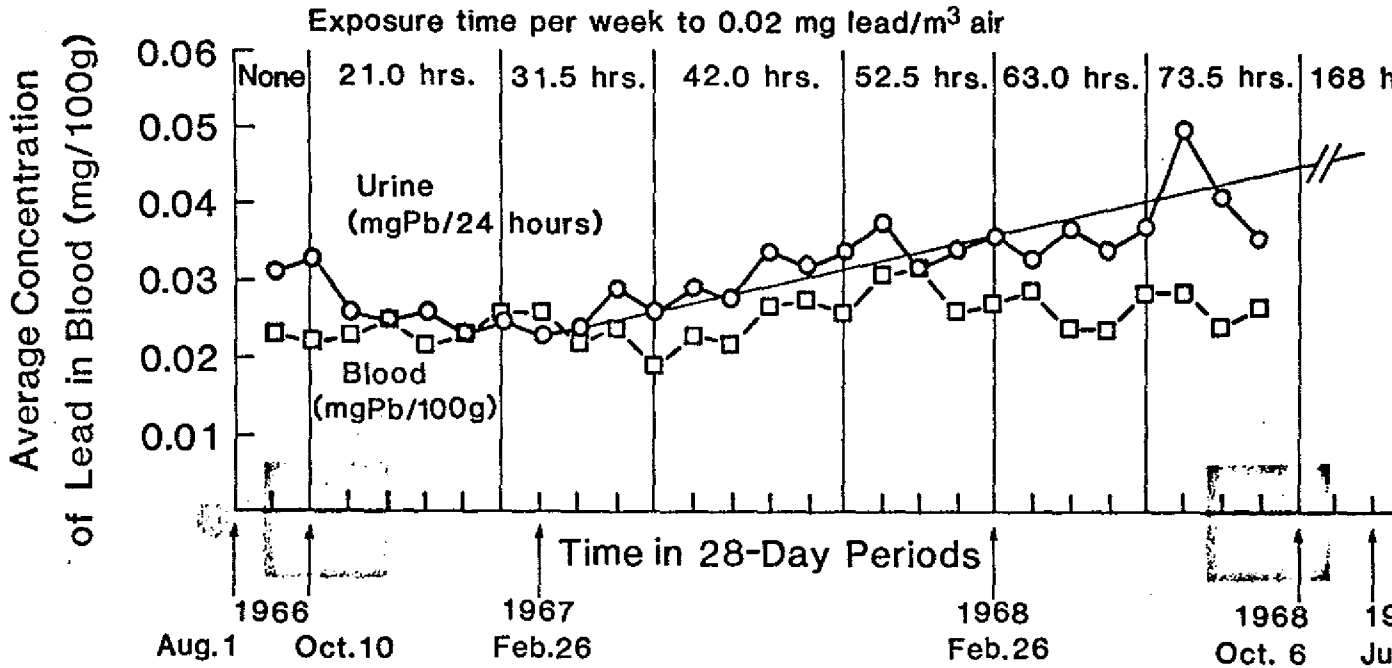


Figure 3.28

Extrapolation of Blood and Urine Levels to Reflect Continuous Inhalation Exposure (Subject S



expression of the effect of continuously breathing ambient air containing 0.02 mg lead/m^3 air in the form provided in the experiment. This line and its projection have not been determined by calculation, and therefore may not be regarded as precise, but the outcome of the projection, even as an approximation, points to the unacceptability of 0.02 mg lead/m^3 air as the threshold value for the ambient air. Thus, by extrapolation, it is predicted that under the experimental conditions, the average lead content of the urine will have reached the high point of its normal range in approximately 4.5 years. In other words, the average output of lead per day in the urine will have shifted from somewhat less than 0.03 mg to approximately 0.08 mg during this time period. After that time, the minimum increase in the rate of excretion will continue at an equivalent rate and will be accompanied by a somewhat slower increase in lead concentration in the blood, as a manifestation of an increase in the body burden of lead.

In contrast to the renal response to the experimental exposure, the concentration of lead in the blood during the experiment was strikingly different. The behavior of the urine and the blood was apparently parallel during the period when the duration of the exposure was 42 hours per week; it continued so during the first half of the next period covering 52.5 hours per week. But from this time on, after a fairly sharp decrease (actually a drop of only 7 micrograms, or about 25 percent per 100 g of whole blood), there was no further consistent increase. Evidently the lead content of the "soft tissues" of the body sustained little or no further significant increase within the period of time represented in the experiment. This phenomenon has been observed previously in connection with elevations of the absorption of lead at rates near the threshold of

detection. It seems that the available lead was diluted (a few milligrams distributed into the kilograms of soft tissue) because of the excretion of lead in transit; this was augmented by the selective absorption of lead into the skeleton, which effectively diminished the rate of the accumulation of lead in the soft tissues.

The results of these experiments seem clear. Their interpretation in relation to the promulgation of a standard for the lead content of the atmosphere is not quite so simple, since it involves careful consideration of all of the information that can be gleaned from the experiments. It is evident that the concentration of 0.02 mg lead/m^3 air, in the form employed in these experiments, would not be tolerated indefinitely by the human population. Such respiratory exposure to lead, combined with lead ingestion from food and beverages in the human diet, will result in an increase in the body burden of lead in the average person. In all likelihood, as judged by earlier experimental results, this increase would be of an indefinitely progressive type. While the consequences of such a slow accumulation of lead in the body throughout the lifetime of the individual and that of a human population are by no means predictable (since no such situation has ever been examined carefully in the course of human history), they can hardly fail to be potentially hazardous. No such hazard would be acceptable.

SUMMARY AND CONCLUSIONS OF THE LEAD INHALATION EXPERIMENTS

The 15 lead inhalation experiments described in this chapter were conducted over a 21-year period from 1950 through 1971. A number of significant findings concerning lead absorption and retention after lead is inhaled were made. Most of these findings were discussed in detail in this chapter; they are summarized below for the convenience of the reader. In addition, a summary and discussion of the subclinical health effects that were identified during the experiments are also included in this section.

The initial goal of the experimental series was to determine the maximum concentration of respirable inorganic lead particles that could be inhaled continuously throughout a lifetime without resulting in a significant lead body burden. Before this goal was reached however, additional conclusions were drawn. By exposing healthy human subjects to known concentrations of particulate lead while quantifying the amount of lead each subject ingested, a lead input/output/retention balance was determined. It was found that the urinary output of lead increased in response to the inhaled dosage. When the subjects' inhalation exposures in the chamber were scheduled to simulate a traditional 40-hour workweek, urinary lead output rose to an elevated level when compared with the control period, and then leveled out to maintain an essentially horizontal curve that was significantly above the control period baseline. This steady level of urinary lead excretion was in sharp contrast to the sustained upward sloping curve that represented the urinary lead excretion of subjects who ingested known dosages of lead.

The experimentally determined leveling off of urinary lead excretion has also been noted in workers who are occupationally exposed

to lead. This is a result of the significant decrease in lead inhalation exposure when the employee leaves the workplace. During these 16-hour periods of comparatively low lead exposure, the worker's output of lead exceeds his intake, and a 24-hour balance is eventually achieved.

However, the results of Experiment 3 indicated that large airborne lead particles are swallowed when they impinge on surfaces in the upper respiratory tract. This ingested lead becomes available for alimentary tract absorption; the continued presence of lead in the body results in a progressive increase in absorption and a corresponding increase in urinary lead excretion. The observed leveling off of the urinary excretion of lead when subjects were exposed to small particles of airborne lead (50 percent <0.005 micron, 90 percent <0.17 micron) on a schedule simulating a 40-hour workweek was not noted when subjects inhaled larger lead particles (50 percent <0.9 micron, 90 percent <2.0 micron, maximum 4.0 micron) on the same schedule. Instead, a steadily rising pattern of urinary lead excretion was observed that showed no sign of tapering off and leveling out. Thus, when a significant portion of the inhaled lead particles are greater than 1 micron in diameter, lead is absorbed from both the respiratory and the alimentary tracts, resulting in a potentially much larger body burden of lead. This fact must be kept in mind by industrial hygienists and plant supervisors.

After completing 10 of the 15 experiments, it was evident that the initial goal of determining the maximum "safe" airborne concentration of lead had been reached. It was determined that there was no hazard of lead poisoning associated with the inhalation of a fully respirable and absorbable inorganic lead compound in the concentration of 0.15 mg/m^3 air, over a period of almost two years. This finding was made under

conditions simulating industrial exposure with the exception of the strict exposure uniformity of the experiment, the virtually complete elimination of lead ingestion in connection with the day's work, and the comparatively low respiratory ventilation rates resulting from confinement within the chamber. Under these exposure conditions, the peak lead concentrations in the subjects' blood and urine were 0.045 mg/100 g and 0.074 mg/liter, respectively. It is believed that since no lead poisoning will occur while the lead concentration in the blood remains below 0.08 mg/100 g, 0.15 mg/m^3 of airborne lead is a relatively safe level of exposure during a 40-hour workweek.

The airborne lead concentration of 0.15 mg/m^3 air was chosen to determine a response gradient in human subjects (Experiments 8, 9, and 10). The results of these experiments allowed the conclusion that if exposure to this concentration of lead is continuous (i.e., 168 hours per week), then the blood lead concentration could reach the level of approximately 0.16 mg/100 g in somewhat less than two years of exposure. Thus, the influence of the discontinuity of lead exposure inherent in the 40-hour workweek schedule is undeniably important.

Experiments 11 through 15 were designed to determine the highest concentration of airborne lead to which a normal individual might be subjected continuously without incurring a measurable increase in the lead concentration in blood or urine. This presumably would also be the concentration that would not significantly increase the body burden of lead. No significant increases in blood or urinary lead concentrations were measured when subjects were exposed to 0.01 mg lead/m^3 air; when subjects were exposed to 0.02 mg lead/m^3 air, an increase in the rate of urinary lead excretion was noted for exposure periods of 42 hours per

week. No demonstrable increase was noted when only 21 hours per week were spent in the chamber. When the weekly exposure was increased to 73.5 hours per week at the same concentration, it became obvious, when extrapolated over the lifetime of the individual, that this exposure would result in a slow accumulation of a potentially harmful amount of lead in the body.

During the 21-year period of experimentation, the subjects received weekly medical examinations. These examinations served the primary purpose of ensuring the continued health of the subjects. However, the medical records are also valuable in that some trends in the subjects' experimental results can be identified. The medical evaluations included measurements of the following: weight, respiration, blood pressure, pulse rate, right-and-left-hand strength (dynamometer readings), stippled erythrocyte count, reticulocyte percentage, urinary porphyrin excretion, and delta-aminolevulinic acid (ALA) excretion. As would be expected, no significant changes were noted for most of these factors. However, the factors (i.e., stippled erythrocyte count, reticulocyte percentage, urinary porphyrin excretion, and ALA excretion) considered to be potential indicators of lead intoxication are discussed.

Changes in the blood have long been recognized as indicators of both early-and-late-stage lead poisoning. Chemical alterations induced by lead, although not entirely specific, represent interferences with enzyme systems that are active in the synthesis of hemoglobin, and hence are among the more subtle influences exerted by the absorption of lead in sufficient amounts and at sufficient rates.

The monitoring of the subjects' basophilic granulation or stippling of the erythrocytes during the course of the 15 experiments

reinforced the growing consensus that this procedure is an unsatisfactory and outmoded clinical method of identifying lead absorption. Figure 3.29 compares the subjects' mean stippled erythrocyte count per 50 fields during their control periods (C), exposure periods (E), and post-exposure periods (P). Also shown in the figure are the mean daily amounts of ingested lead during these periods, since ingested lead was found to strongly influence the total amount of lead that was absorbed. It was concluded from these results that the phenomenon of stippled erythrocytes is not a specific sign of lead absorption. Since it does not vary quantitatively with either the rate of absorption or the amount of lead absorbed, it is a poor substitute for determining the concentration of lead in the blood or the urine.

Reticulocytosis is another common but nonspecific finding in lead poisoning cases. However, as shown in Figure 3.30 a high degree of correlation between exposure to airborne lead particles and this condition was not found. In fact, a comparison of the mean percentages of reticulocytes measured during subjects' control (C), exposure (E), and post-exposure (P) periods shows that there was often a significant drop in this factor when a rise was expected, even when the mean amounts of lead ingested were taken into account.

As graphically shown in Figure 3.31, the lead concentration changes in the blood proved to be much more reliable than the other hematologic changes involving stippled erythrocytes and reticulocytosis.

The concentration of lead in the blood of the person who has been exposed to inorganic lead is the most important single piece of evidence required to portray the significance of absorption of lead. Since the concentration of lead in the blood varies only within extremely narrow limits from hour to hour and from day to day (except under

Figure 3.29

Mean Stippled Erythrocyte Count and Mean Daily Alimentary Lead Intake

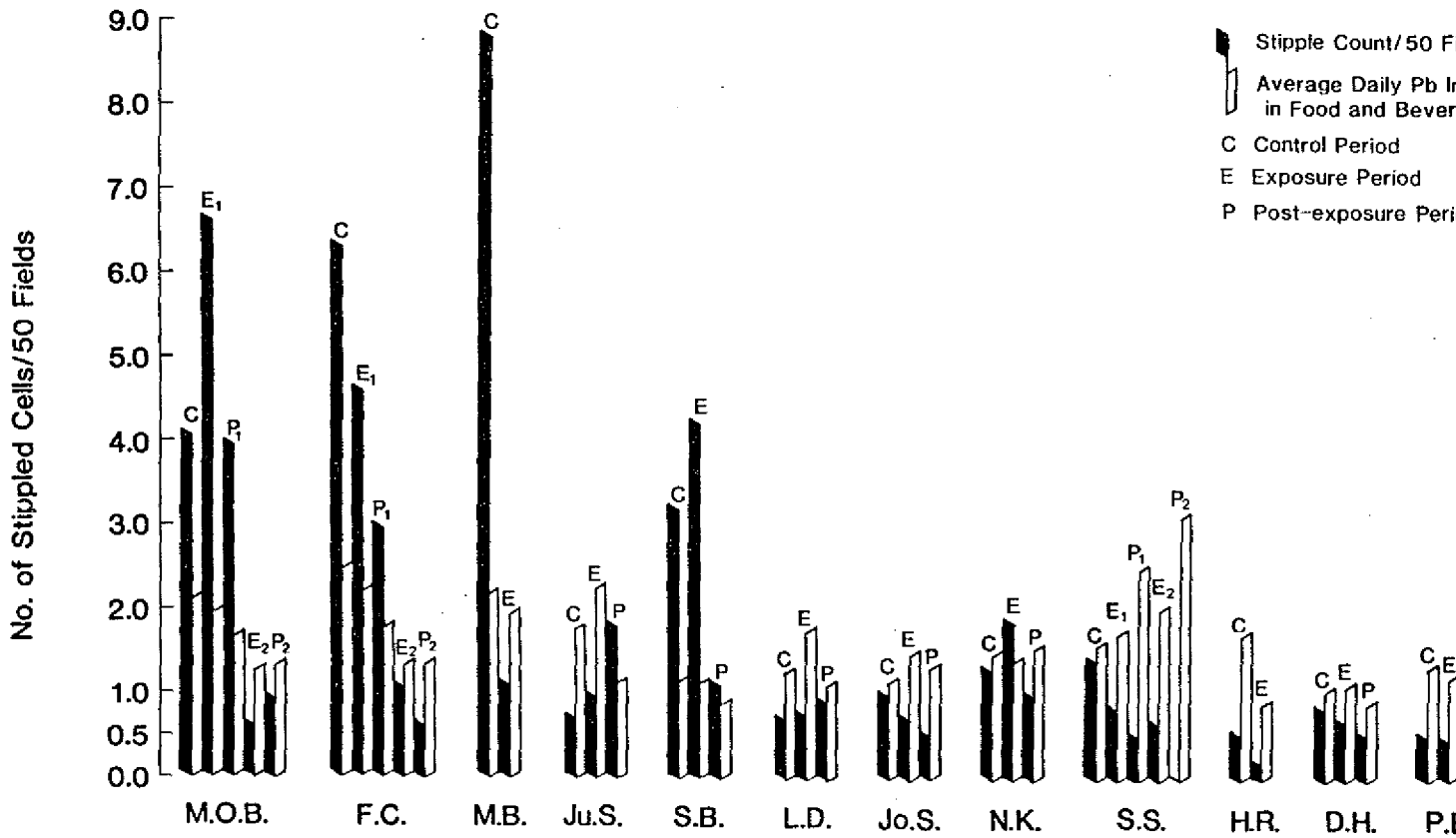


Figure 3.30

Mean Percentages of Reticulocytes and Mean Daily Alimentary Lead Intake

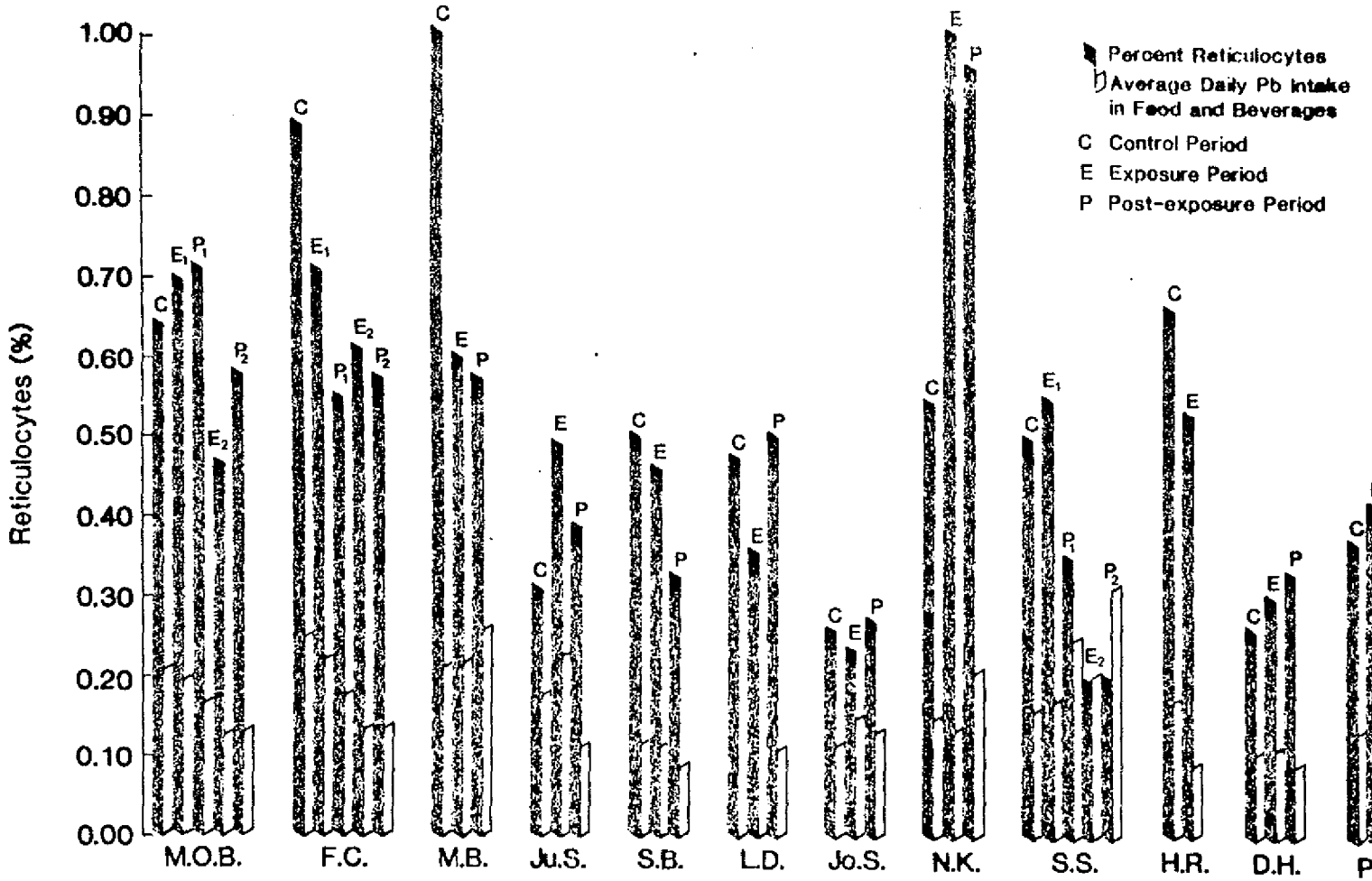
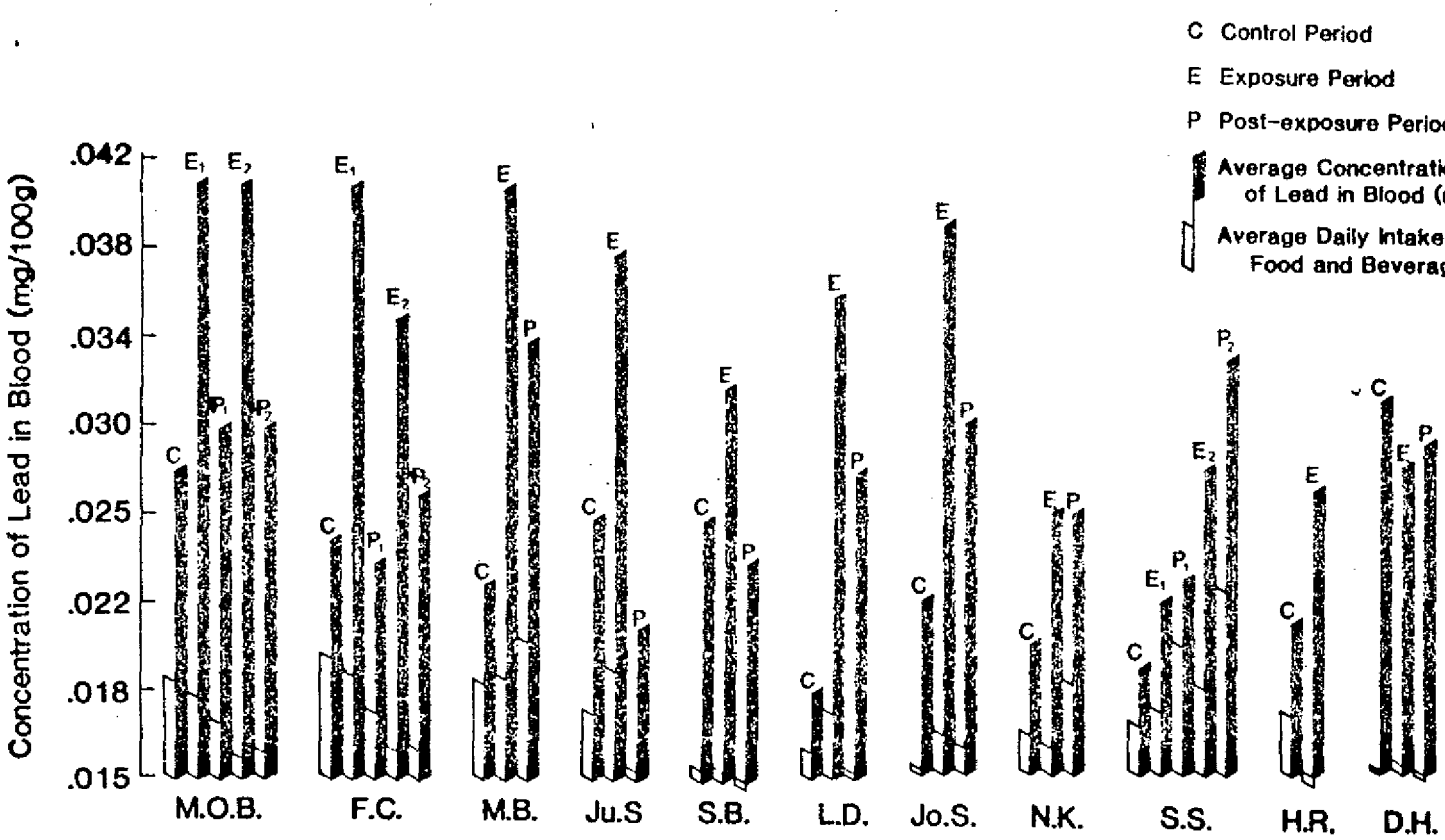


Figure 3.31

Mean Concentration of Lead in Blood and Mean Daily Alimentary Lead Intake



conditions involving concurrent and highly variable exposure to lead), only one determination would be required for diagnostic purposes were it not for the possibility of the contamination of a sample of blood with minute quantities of lead in the processes of its withdrawal and analysis. Because of these possibilities, even under the best of conditions, it is advisable to obtain multiple samples (at least in duplicate) and to submit them for separate analysis. The results should check within the very narrow limits of a few micrograms when expressed in terms of 100 grams of whole blood if they are to be accepted as reliable.

When properly carried out, the determination of the rate of the urinary excretion of lead provides specific and invaluable information on the extent and significance of the lead absorption of an individual. The simplest combination of materials for diagnostic purposes, and one that will serve to eliminate most of the errors of sampling and interpretation, constitutes duplicate samples of blood taken by an instructed person using special equipment. Additionally, one or more "spot" samples of urine, each voided directly into the container specifically provided for the purpose and under the critical eye of an instructed person, should be obtained. Analytical and physiologic concurrence on the part of these results will stamp them as valid, while variation among them beyond the known ranges of analytic precision or physiologic limitation creates the demand for further investigation.

The significance of porphyrinuria, in relation to the diagnosis of lead intoxication, is considerable. However, abnormal quantities of porphyrins, chiefly coproporphyrin III, appear in the urine as an expression of a derangement of the synthesis of hemoglobin in a number of diseases, including lead poisoning. The presence of excessive porphyrin in the

urine seems to be among the first evidences of lead intoxication. Since the goal of industrial hygiene in the lead-using industries is the prevention of lead intoxication, reliance on this incipient sign of intoxication as a means of recognizing and terminating hazardous exposure to lead prior to the appearance of more serious manifestations would seem to be considerably less than satisfactory. Figure 3.32 displays the mean daily coproporphyrin III excretion during the control (C), exposure (E), and post-exposure (P) periods of the lead inhalation subjects. Also shown are the corresponding mean daily lead ingestions. Examination of this chart indicates that when lead exposure levels are so low that lead intoxication does not result, the amount of urinary coproporphyrin III excreted may not be a significant indicator of absorption.

Investigators have found that increased quantities of delta-aminolevulinic acid (ALA) appear in the urine prior to an increase in coproporphyrin III therein, and also that the former occurs in the urine in an earlier stage of the absorption of lead (at lower levels of lead concentration in the blood) than does the latter. Hence, for the early detection of potentially dangerous absorption of lead, especially for purposes of preliminary screening prior to analysis of the blood, determination of the concentration of lead in the blood is preferable to either of these. Figure 3.33 depicts the correlation found between the mean concentration of ALA in the urine of the two subjects whose examinations included this analysis and in the initiation of their lead exposure periods. However, Figure 3.34 shows the superiority of the measurement of urinary lead excretion in relation to both ALA and coproporphyrin III determinations.

Chapter 4 summarizes the conclusions reached from all of the inhalation and ingestion experiments.

Figure3.32

Mean Daily Urinary Coproporphyrin Ⅲ Excretion and Mean Daily Alimentary Lead Intake

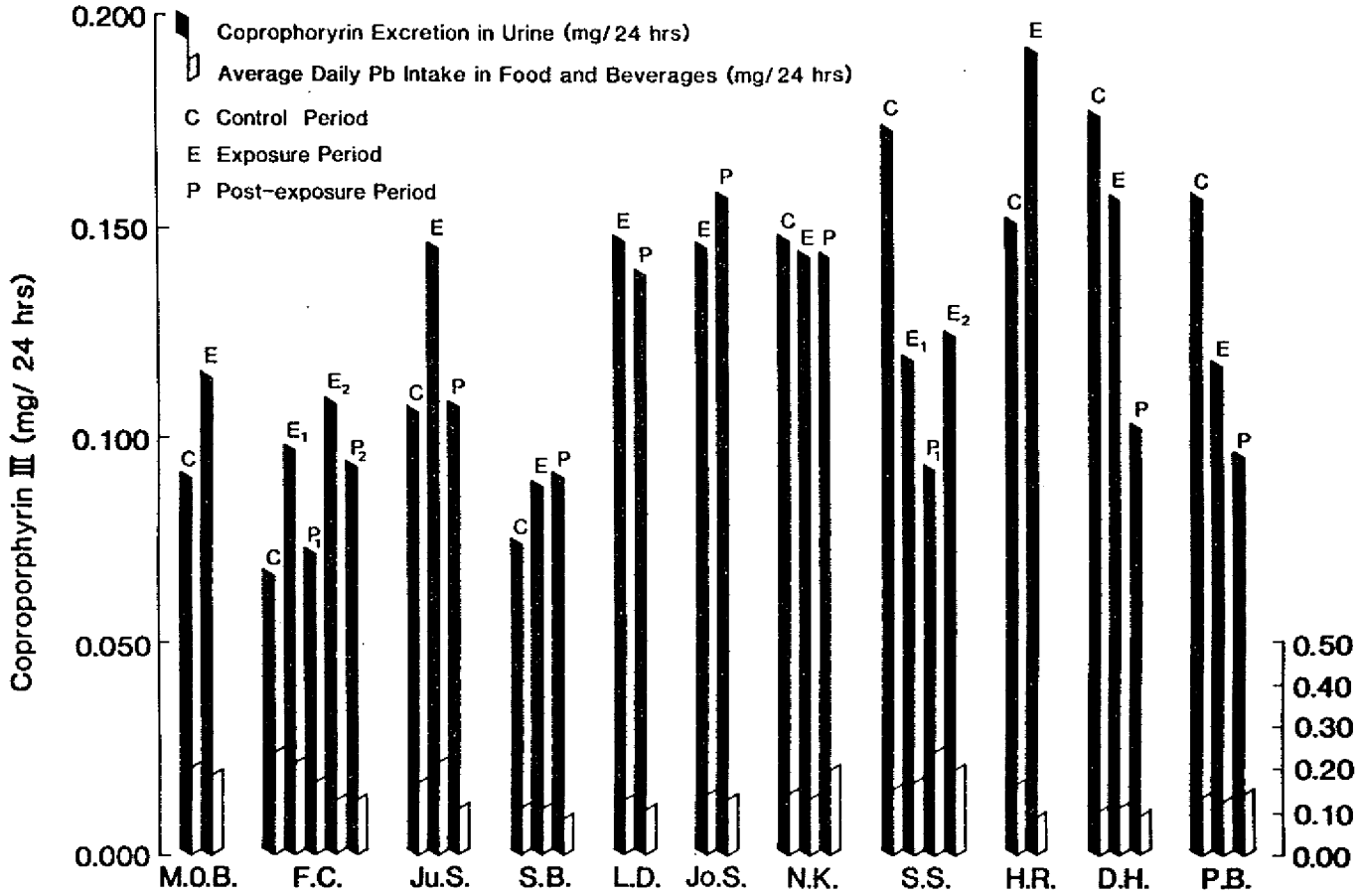


Figure 3.33

Mean Daily ALA Output and Mean ALA Concentrations in Urine

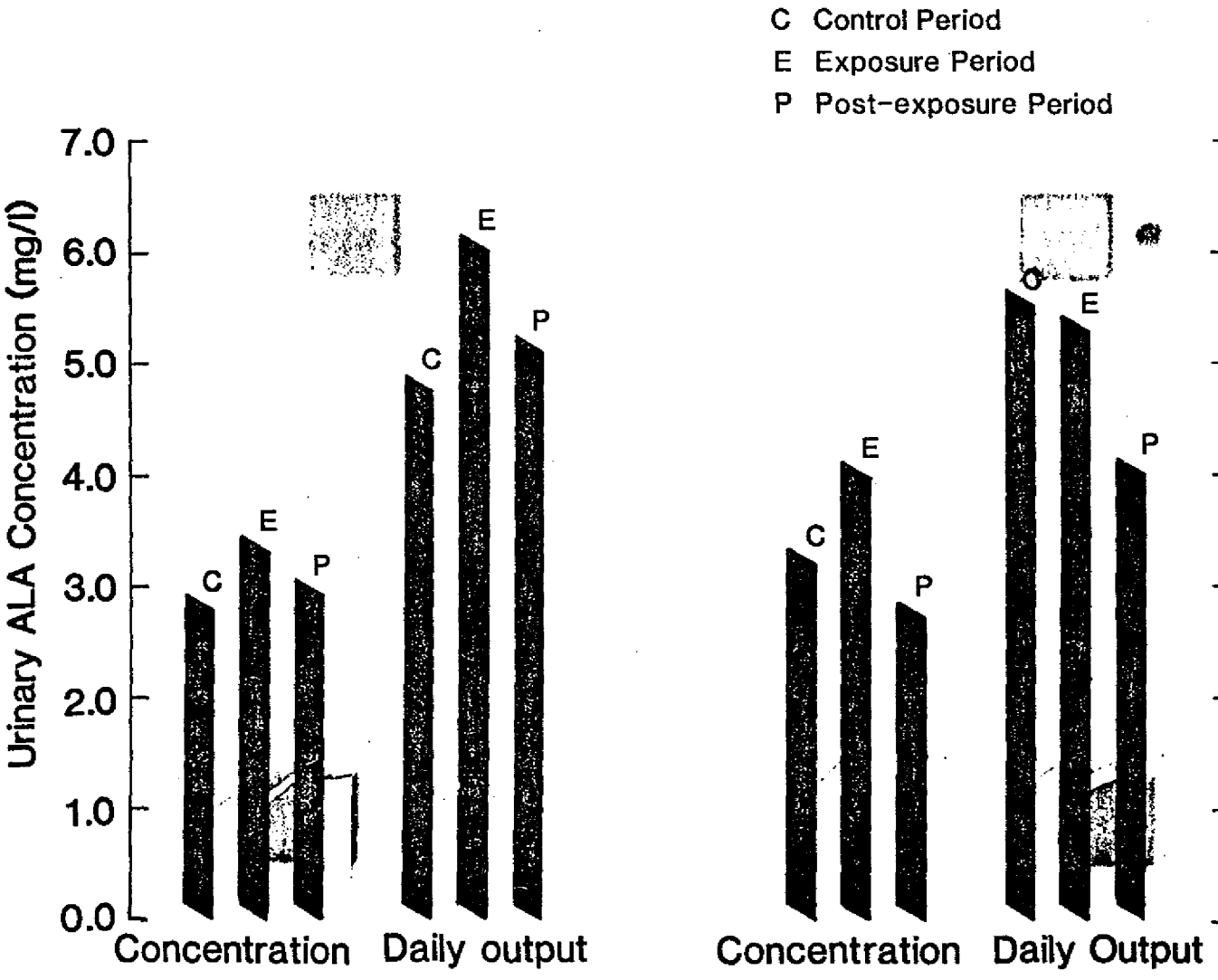


Figure 3.34

Mean Daily Output of Lead in Urine and Mean Daily Alimentary Lead Intake