Brit. J. industr. Med., 1966, 23, 263

Urinary Screening Tests to Detect Excessive Lead Absorption*

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PART I: A COMPARISON

The biological variation encountered in spot urine samples was assessed by collecting six sets of serial urine specimens from five men. The lead, coproporphyrin, and creatinine contents of each specimen were determined and the specific gravity was measured. It is found that as the mean concentration of the metabolite rises so the variability of the individual values increases. The scatter of the concentrations is not significantly different from that found in the rates of excretion. Adjustment of the figures to either a constant specific gravity or creatinine concentration increased the scatter. The effect of the diurnal cycle on the variability is negligible as the spread of the combined results is uniform over the 24-hour period.

The results of spot urine samples must be considered collectively before they can indicate the mean excretion level.

Twenty-four-hour urine samples were obtained from 23 lead-intoxicated men before and throughout their treatment with chelating agents. The initial excretion of lead during intravenous infusion of disodium calcium ethylenediaminetetra-acetate (first Pb EDTA) and the weight of lead excreted as the complex, before the coproporphyrin excretion falls to a normal level (less than 100 μg. per day), termed the 'excess' lead, are used as objective measures of the lead absorption. These two indices are linearly related to the pretreatment urinary levels of lead and coproporphyrin, regardless of whether the results are expressed in μg. per litre or μg. per day. Due to the environment having an effect on the urinary concentrations it is concluded that in general the weight of metabolite excreted in the 24-hour period possibly provides the more reliable guide to the lead absorption of the individual.

The measurement of the lead or coproporphyrin content of urine samples is the usual screening test used throughout industry. When a number of people are employed in the same environment the results can be used in two ways. Hamlin and Weber (1947) and Zielhuis (1961a) have shown that the average urinary lead or coproporphyrin concentration of a group of men indicates the atmospheric lead concentration to which the group is exposed. Thus by measuring the group average lead and coproporphyrin excretions at regular intervals the lead hazard can be monitored with a reasonable degree of accuracy. The absorption of lead by the individual is assessed by comparing the concentration of each specimen against the maximum urinary concentration (M.U.C.). The M.U.C. is defined as the highest concentration which can be found in the urine without damage to health. Unfortunately there is a considerable divergence of opinion as to the level of the M.U.C., which is in part due to differing definitions of 'health'. Moreover, Buchwald (1964) pointed out that there is some disagreement concerning the collection of the specimen and the manner in which the results of urine analysis should be expressed. It is well known that urine specimens show biological variation, the greatest variability being associated with the results from single voidings.

It appears that although the atmospheric pollution can be satisfactorily monitored by urine analysis the protection afforded to the individual is uncertain.

It is the object of this paper to compare the efficacy of the various factors which are considered when the results of urine analysis are used to assess the degree of lead absorption. For convenience, this work is divided into a consideration of the results of single voidings and of cumulative samples.

Received for publication February 4, 1966.

*This paper is based on part of a thesis submitted for the degree of Master of Science in the University of Newcastle upon Tyne (1965).

Variability of Single Voidings of Urine

Most firms rely on the analysis of spot specimens of urine for their screening tests. These show extreme variability and several methods have been suggested to reduce this scatter. It has been proposed that corrections should be made for the time over which the urine is excreted (Barnes, 1939), the volume (Kehoe, Cholak, Hubbard, Bambach, McNary and Story, 1940), a combination of time and volume (Pinto, Elkins, and Ege, 1941), the specific gravity (Levine and Fahy, 1945), and the creatinine concentration (Smith and Kench, 1957). Molyneux (1964) has proposed that the specimen should be collected at a specified time of day.

This investigation was carried out to determine three things: first, the extent of the variation encountered in spot urinary lead and coproporphyrin concentrations and excretion rates; secondly, the value of adjustment for specific gravity and creatinine in reducing the scatter; and finally, the contribution of the diurnal rhythm to the variability.

Experimental Data It is difficult to collect serial urine specimens from active leadworkers. For this reason consecutive specimens were obtained from five hospital in-patients. The men had all had an industrial exposure to lead and showed clinical evidence of excessive absorption. A set of specimens was collected from each man before he was treated with chelating agents. A further set was provided by one of the men while he was convalescing one week after therapy. When the volume was sufficient each sample was analysed for lead (Dick, Ellis, and Steel, 1961), coproporphyrin (Rimington and Sveinsson, 1950), and creatinine content (Varley, 1962). The specific gravity was measured and the time of each voiding was recorded.

The experimental data are given in the Appendix to this paper (p. 276). Each figure in the Tables represents the mean of duplicate or, in the case of lead, triplicate analyses. The 'mean concentration' of each metabolite was determined for each series. This 'mean concentration' was calculated as the total weight of the constituent excreted divided by the total volume of urine collected, *i.e.*, the result of a single cumulative sample (this value will be placed in inverted commas throughout the remainder of the paper). Thus the arithmetical average of the spot values does not necessarily equal the 'mean concentration'.

In Figs. 1a and 1b the lowest and highest readings of the lead and coproporphyrin concentrations are plotted against the 'mean concentration'. It is apparent that the spread of the results for each man is increased if his 'mean concentration' is high. The highest readings are about 10 to 20 times the lowest. These findings are in agreement with those of previous workers (Rainsford, 1961; Elkins, 1961; Molyneux, 1964; and others). It is obvious that the variability associated with single voidings of urine is too great for any one figure to give a reliable indication of the excretion level.

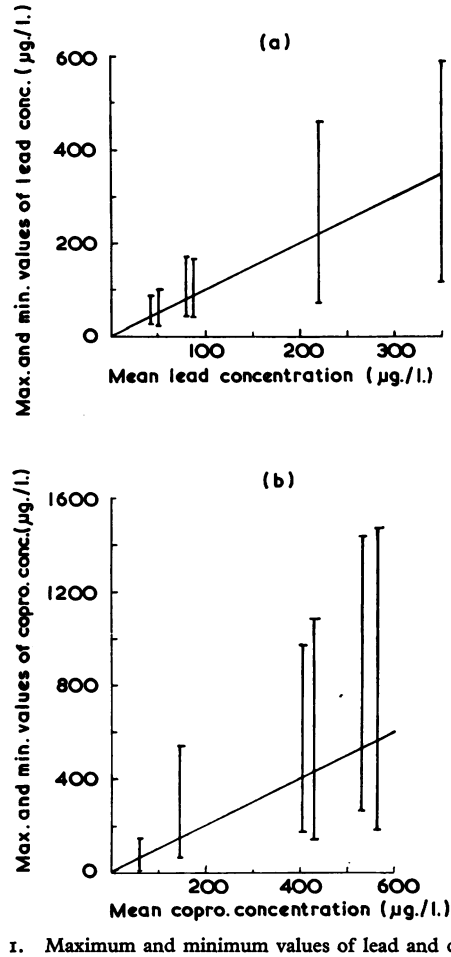

FIG. 1. Maximum and minimum values of lead and coproporphyrin (µg./litre) plotted against the 'mean concentration' (µg./litre).

To be of practical value, any method for reducing the spread of spot results must either be applicable in all cases or used only within easily defined limits. The original proposal of Levine and Fahy (1945) that all urine concentrations should be reported adjusted to a constant specific gravity of 1·024 has been modified by several investigators. Rainsford (1961) and Buchwald (1964 and 1965) recommended that a standard specific gravity of 1·016 was more appropriate for British workpeople. Schoen,

Young, and Weissman (1959) thought that the specific gravity, as a measure of the renal concentrating ability, is only valid when the specific gravity exceeds 1·020. Price, Miller, and Hayman (1940) showed that the estimation of total urinary solids from the specific gravity is only valid for urines of the same relative composition and that spot specimens are inaccurate due to variations in the solids content. These and other criticisms have led to several investigators suggesting the creatinine concentration as a reference point. However, Bleiler and Schedl (1962), who measured the variability of the creatinine content in 24-hour collections of urine, concluded that the use of creatinine excretion as a reference in interpreting the excretion of other metabolites may be invalid when based on single voidings.

So that the results for the different men and the value of adjustment for specific gravity and creatinine can be compared, each value of the lead and coproporphyrin concentrations was expressed as a proportion of the 'mean concentration' of the series. The lead and coproporphyrin concentrations were adjusted to a constant specific gravity of 1·016 and expressed as a proportion of the 'mean concentration' according to the equation:

$$\text{Usg} = \frac{U_o \times G_s}{G_o} \times \frac{100}{M}$$

where Usg is the adjusted proportionate value, U_o is the observed concentration (μg./litre), G_s is (standard specific gravity − 1) × 1000 = 16, G_o is (observed specific gravity − 1) × 1000, and M is the 'mean concentration' (μg./litre). In a similar fashion the lead and coproporphyrin proportions were adjusted to the 'mean creatinine concentration' of the series by the formula:

$$\text{Ucr} = \frac{U_o \times Cr_s}{Cr_o} \times \frac{100}{M}$$

where Ucr is the adjusted proportionate value, U_o is the observed concentration (μg./litre), Cr_s is the 'mean creatinine concentration' (g./litre), Cr_o is the observed creatinine concentration (g./litre), and M is the 'mean concentration' of the metabolite (μg./litre). The rates of excretion were also expressed as proportions of the average rate of excretion. All proportionate values are included in the Appendix (p. 276).

The individual sets of proportionate values can be pooled to form a combined set. The variability of the individual and combined sets of proportions, measured as the coefficients of variation, are shown in Table I.

The opinion that the increase in variability of the specific gravity corrected figures is due to the inclusion of urines of low specific gravity is not substantiated in this investigation. Patients C and P2 excreted urines ranging from S.G. 1·004 to 1·016 and S.G. 1·004 to 1·020 respectively. Specific gravity adjustment of C's results reduced the lead and coproporphyrin coefficients of variation by about a third, whereas in P2's case adjustment increased both coefficients of variation by half as much again. Furthermore, when specific gravity correction was applied to K's results the coefficient of variation of the lead values was increased but the coefficient of variation of the coproporphyrin figures was reduced. Patient P provided a set of specimens before and after treatment with chelating agents (series P and P2). Before therapy both the lead and coproporphyrin coefficients of variation were reduced by specific gravity correction but after medication adjustment increased both coefficients of variation. It is apparent that there is no simple criterion which indicates when specific gravity adjustment would reduce the variability of the concentrations.

The figures expressed as rates of excretion and as

TABLE I

COEFFICIENTS OF VARIATION

Subject	*No. of Samples*	*Lead*				*Coproporphyrin*			
		Observed Result	*Adjusted to*			*Observed Result*	*Adjusted to*		
			Specific Gravity	*Creatinine*	*Rate*		*Specific Gravity*	*Creatinine*	*Rate*
C	13	42·8	25·7	37·1	40·0	54·5	32·6	28·7	**59·9**
K	17	36·0	**54·0**	**59·0**	**73·5**	45·9	31·6	26·8	**48·2**
N	21	43·7	22·7	**66·7**	38·0	48·8	32·5	**87·2**	**33·1**
P	17	32·5	24·6	**46·7**	**52·5**	42·5	28·3	22·4	**34·2**
P2	17	42·5	**62·8**	**51·4**	37·4	54·6	**76·2**	**64·1**	**63·2**
U	21	33·2	31·3	**35·5**	**44·7**	58·9	50·0	39·7	**42·7**
Combined	106	39·5	**48·9**	**56·6**	**43·1**	51·9	**56·1**	**66·6**	**45·7**

The coefficients of variation in bold are higher than the observed.

creatinine corrected proportions show greater variability more frequently than those expressed as specific gravity adjusted values. The coefficients of variation of the combined sets of figures can be compared by Student's 't' test of significance, according to the equation:

$$\text{'t'} = \frac{CV_1 - CV_2}{\sqrt{\frac{(CV_1)^2}{2N_1} + \frac{(CV_2)^2}{2N_2}}}$$

where 't' is Student's 't', CV is the coefficient of variation, and N is the number of items in the coefficient of variation. It is found that the coefficients of variation of the observed proportions are not significantly different from those of either rates of excretion ($P > 0{\cdot}4$ and $P > 0{\cdot}2$ for lead and coproporphyrin respectively) or the specific gravity adjusted coproporphyrin figures ($P > 0{\cdot}4$). The coefficients of variation of the observed proportions are significantly lower than either the specific gravity adjusted ($P < 0{\cdot}05$) or creatinine corrected ($P < 0{\cdot}001$) lead values and the creatinine corrected coproporphyrin values ($P < 0{\cdot}02$).

It appears that correction by any of these methods will reduce the variability of some sets of results. However, the gross increase in variability of the others offsets any advantage in using these techniques as routine control methods.

Turning now to the possibility of a diurnal cycle, it is found that the results for any one man show a rhythmic variation when plotted on a continuous time scale. The urinary lead and coproporphyrin concentrations of each specimen collected from patient K are shown in Figure 2. It can be seen that the lead values tend to rise from midnight to 8.00 a.m. and to fall to a minimum value at about 8.00 p.m. each day. Similarly, the coproporphyrin values rise between midnight and 8.00 a.m. and fall between noon and 6.00 p.m. However, at any given time, the levels alter considerably from day to day. This indicates that neither the amplitude nor the wavelength of the cycle is constant in the man. In Figs. 3 and 4, where the results of each man are plotted on a 24-hour basis, it is apparent that this day-to-day variation obscures the hourly rhythm. Moreover, when all the results expressed as proportions of their 'mean concentrations' are plotted in the same diagram (Figs. 5 and 6) the scatter is equally marked at all times of the day. It seems therefore that, although the diurnal cycle is a component, it contributes only a negligible part of the total variability associated with spot specimens.

These observations are at variance with those of Molyneux (1964). However, the subjects in the present investigation were confined in centrally heated hospital wards and were not allowed any violent exercise. These conditions contrast with those of active lead workers, who are often subjected to an artificial thermal environment, high humidity, and manual labour. In addition, the fluid intake is often restricted to certain periods of the work shift. It seems that these environmental factors, as well as exposure to the hazard, contributed to Molyneux's findings.

It is apparent that the results of a single voiding of urine are in themselves meaningless, regardless of whether or not the specimen is, collected at some specified time, expressed as a rate of excretion or adjusted to either a constant specific gravity or creatinine concentration. Hamlin and Weber (1947) suggested that for the interpretation of spot specimens one has not to be concerned with minutiae but to analyse a sufficient number of collections to arrive

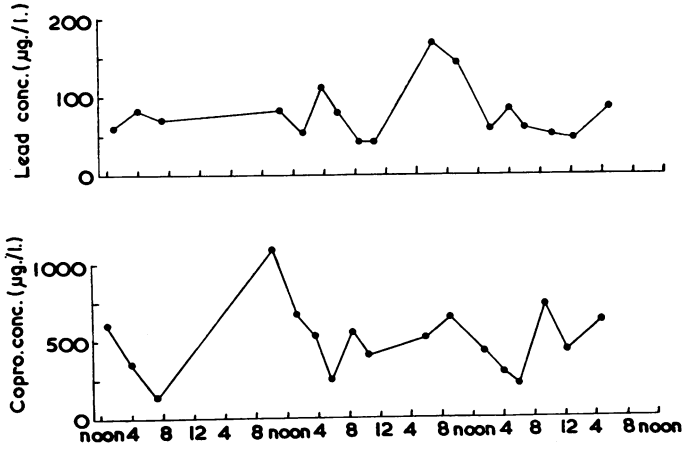

FIG. 2. Diurnal rhythm in urinary metabolite excretion of patient K.

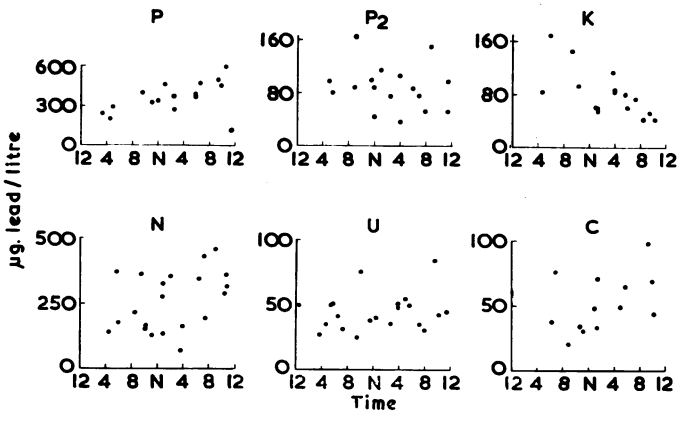

FIG. 3. Individual lead excretions plotted on a 24-hour basis.

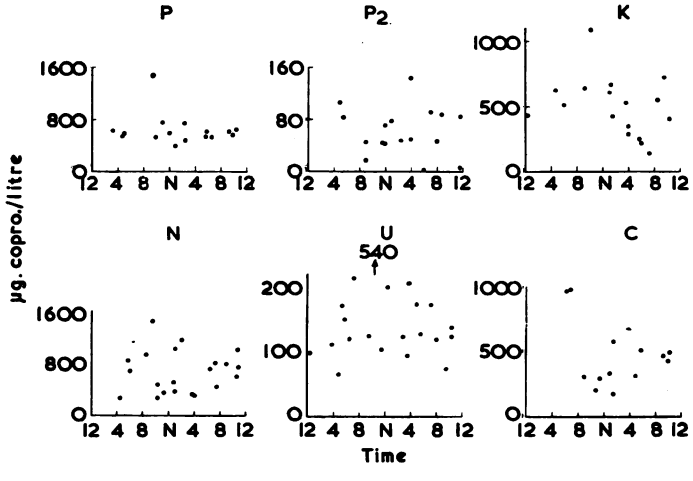

FIG. 4. Individual coproporphyrin excretions plotted on a 24-hour basis.

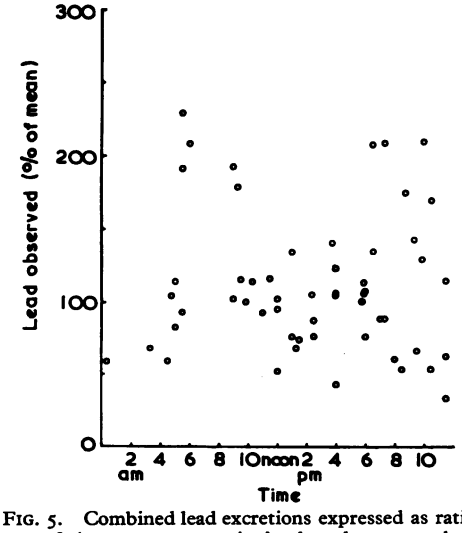

FIG. 5. Combined lead excretions expressed as ratios of 'mean concentration' plotted on a 24-hour basis.

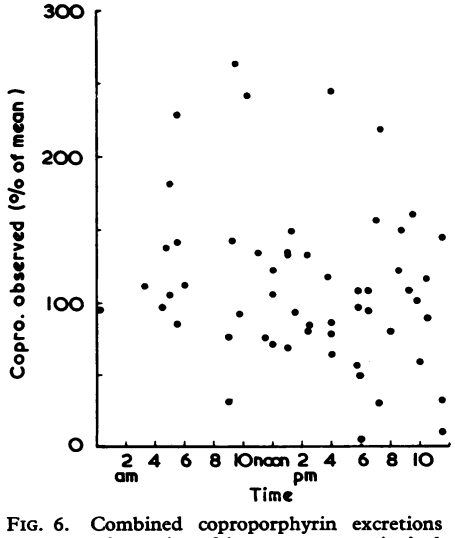

FIG. 6. Combined coproporphyrin excretions expressed as ratios of 'mean concentration' plotted on a 24-hour basis.

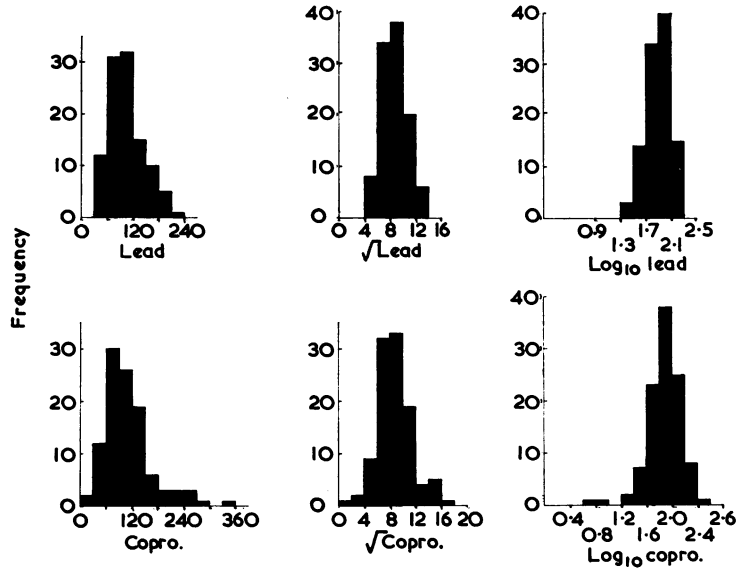

FIG. 7. Transformations of concentrations of lead and coproporphyrin expressed as a proportion of the 'mean concentration' of the man. (Each man contributes between 13 and 21 readings to each distribution.)

at a definite trend. When the scatter of the spot values about the 'mean concentration' is considered, it is found that there are insufficient data from any one man to arrive at a definite conclusion as to the shape of the distribution. By using the proportionate values, all the figures can be pooled to provide a sufficient number. In Fig. 7 it can be seen that the square roots of the proportions lie in an approximately normal distribution, whereas the proportions and the logarithms of the proportions fall in slightly skewed curves.

If the averages of a number of specimens are taken, these averages will be arranged about the arithmetical mean concentrations in a less skewed distribution, and the variability will be reduced by the factor $1/\sqrt{n}$ where n is the number of results providing the average. Thus, in order to obtain a reliable measure of the excretion level, the spot specimens must be considered collectively. This can be done either by statistical methods or by collecting cumulative samples of urine.

Cumulative Samples

A major difficulty in examining the reliability of cumulative urine samples as a method of assessing the lead absorption is to obtain an objective measure of the lead absorption of the individual. However, an indication can be gained by treating the man with chelating agents. Teisinger and Srbová (1959) and Rieders (1960), among others, have suggested that the lead excretion after the initial intravenous infusion of disodium calcium ethylenediaminetetraacetate (first Pb EDTA) provides a measure of the lead absorption. Cramér and Selander (1965) considered that 'a more or less objective measure' of the lead absorption was provided by the total weight of lead excreted in the urine during treatment with 9 g. oral penicillamine by divided doses. When a leadworker is given chelating agents not only is there a dramatic rise in the urinary lead excretion but there is also a marked fall in the coproporphyrinuria. It appears that the decrease in the coproporphyrin excretion is related to the amount of lead excreted as the complex. A further indication of the lead absorption is thus provided by the 'excess' lead, which is the weight of lead excreted as the complex before the coproporphyrin excretion falls to a normal level (less than 100 μg. per day).

In this part of the work comparisons are made in the relationships between the pretreatment urine analyses and the lead absorption as measured by the first Pb EDTA and the 'excess' lead.

Experimental Data The subjects in this part of the investigation were hospital in-patients who had all been exposed to an industrial lead hazard. They all showed clinical evidence of excessive lead

TABLE II

EXPERIMENTAL DATA

Patient	*Urinary Excretion*				*First Pb EDTA (mg.)*	*'Excess' Lead (mg.)*
	Lead		*Coproporphyrin*			
	μg./24 hr.	*μg./litre*	*μg./24 hr.*	*μg./litre*		
A	395	240	1,415	825	10·1	37·1
B	700	710	1,655	1,670	8·4	54·8
C	100	50	790	405	3·6	10·3
D	840	670	—	—	12·1	—
E	80	90	40	35	—	Nil
F	120	75	415	255	6·8	—
G	51	55	Nil	Nil	0·8	Nil
H	195	125	445	280	5·2	8·9
I	—	—	—	—	6·8	20·3
J	270	150	785	425	8·9	35·4
J2	165	80	280	135	3·2	5·4
J3	93	46	255	125	2·2	2·2
K	100	85	505	435	4·3	17·8
L	540	705	—	—	3·3	—
M	245	600	825	2,010	8·1	22·4
N	360	215	885	530	8·8	33·4
O	415	185	1,870	845	—	29·6
P	565	350	920	565	—	24·2
Q	160	105	90	60	—	Nil
R	165	80	395	190	3·7	6·0
S	280	95	260	85	—	6·2
T	245	195	420	330	6·1	10·4
U	125	60	295	140	5·7	5·7
V	220	160	410	295	5·7	12·2
W	145	51	125	40	3·2	4·6

absorption. The 23 men were treated with intravenous infusions of disodium calcium EDTA. In addition, two men received oral disodium calcium EDTA and a further five men were given oral penicillamine medication. Twenty-four-hour urine samples were collected from each man before and throughout the regimen. The collections were timed to coincide with the administration of the drugs. The lead and coproporphyrin content of each sample was measured.

In Table II are shown the results of the analyses. The pretreatment lead and coproporphyrin levels are expressed in two ways: first, as the average excretion in μg./24 hours and secondly as the mean concentration in μg./litre. The pretreatment levels can be considered as screening tests since these values could have been measured while the man was in employment. The relationships between the screening tests and the first Pb EDTA and the 'excess' lead are shown as scatter diagrams in Figs. 8 and 9.

The results of correlation analyses (Table III) reveal that the excretion levels of lead and coproporphyrin indicate both the first Pb EDTA and the 'excess' lead. It is useful to consider which mode of expression of which metabolite provides the more reliable guide to the lead absorption. In Table III it can be seen that the results expressed as the daily excretions (μg./24 hours) have higher correlations than those expressed as concentrations (μg./litre). Furthermore, the coproporphyrin correlation coefficients are higher than the corresponding lead values. To determine whether these differences are statistically significant, each correlation can be compared with all the others by an application of Duncan's multiple comparison method (James, 1964). It is found that the 36 comparisons evolved from the nine correlation coefficients show no significant differences. This observation demonstrates that the degree of lead absorption is equally reflected by the lead and coproporphyrin urinary excretion levels, regardless of how the results are reported. Statistically significant differences might, of course, emerge if more patients were included in further studies.

The practical application of the above conclusions will now be considered. The hospital patients who provided the specimens were living under carefully

TABLE III

RESULTS OF CORRELATION ANALYSIS

Screening Test	*First Pb EDTA*			*'Excess' Lead*		
	n	*r*	*P*	*n*	*r*	*P*
Lead (μg./24 hr.)	19	+0·69	<0·01	21	+0·84	<0·001
(μg./litre)	19	+0·51	<0·05	21	+0·73	<0·001
Coproporphyrin (μg./24 hr.)	17	+0·77	<0·001	21	+0·88	<0·001
(μg./litre)	17	+0·62	<0·01	21	+0·74	<0·001
First Pb EDTA (mg.)				17	+0·82	<0·001

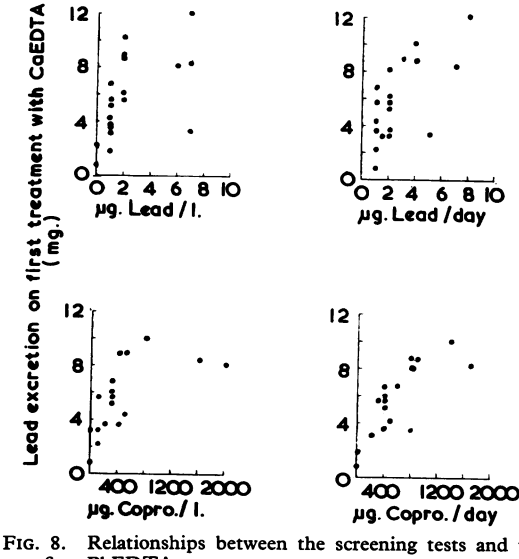

FIG. 8. Relationships between the screening tests and the first PbEDTA.

regulated conditions of environment, diet, fluid intake, etc. These conditions do not apply to active leadworkers. Molyneux (1964) demonstrated that the time a person spends at work influences the urinary concentrations of metabolites. Hence the values of the concentrations of workers will be different from those of hospital in-patients. Furthermore, given a constant exposure (in time and concentration) in two groups of men, the urinary concentrations of men working in comparable environmental conditions will be similar but the level will be different from that of men working under different environmental conditions. Hence a maximum urinary concentration deduced from men in one set of circumstances cannot be used to safeguard the health of all men working under any conditions. On the other hand, Cantarow and Trumper (1955) found that the normal kidney excretes the required amount of solids regardless of the quantity of water available (within wide limits) for their solution.

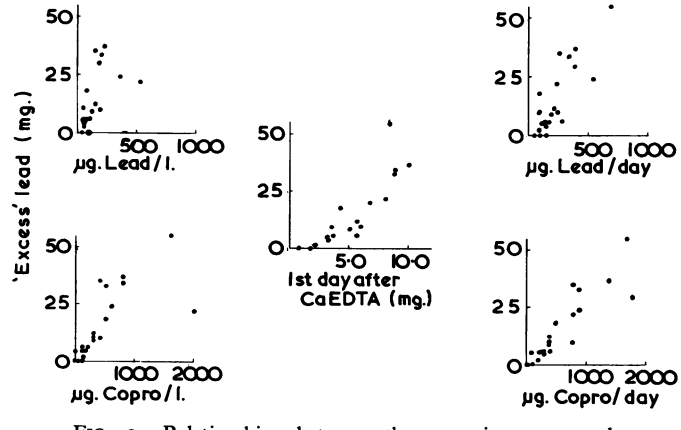

FIG. 9. Relationships between the screening tests and 'excess' lead.

Therefore, it is valid to compare the daily excretion levels of men working under different conditions.

In conclusion it can be stated that, unless they are considered collectively, the results of single spot specimens are too variable to indicate the excretion levels of the metabolites. The urinary concentrations of lead and coproporphyrin, of people in comparable environmental conditions, reflect the lead absorption. The daily weight of metabolite eliminated possibly provides the more reliable guide to the lead absorption as the effects of environmental factors on the concentration are reduced.

PART II: INTERPRETATION OF THE DATA

It is suggested that leadworkers can be protected against absorbing an excessive quantity of lead by observing changes in the urinary excretions of lead or coproporphyrin. The collection of urine and the method of reporting the results should be standardized within each factory. A simple statistical method is described by which the mean excretion level and significant changes in that level can be deduced.

In 1949 Lane pointed out that, when the lead absorption of a group of men exceeds a certain level, cases of plumbism are likely to occur, but not necessarily in those individuals with the higher lead concentrations in the urine. Furthermore, Zielhuis (1961b) found that if the maximum urinary concentration for coproporphyrin was taken as 4 on the 'Donath scale'—equivalent to 400 μg./litre—although 83% of workers with a haemoglobin concentration of less than 12·8 g./100 ml. would be detected, 11% of those with a haemoglobin level of more than 14·7 g./100 ml. would also be compelled to discontinue their exposure. In Table II it can be seen that patient W passed urine of which both the lead and coproporphyrin content fell within the non-exposed range, *i.e.*, less than 60 μg. lead and 120 μg. coproporphyrin per litre of urine. Yet this same man exhibited several clinical signs and symptoms of excessive lead absorption. It seems that there is no lower limit for excreted metabolites below which clinical evidence of excessive lead absorption does not appear. This implies that to provide adequate protection for all men each man must be considered separately.

It can be assumed that the urinary excretion levels of lead and coproporphyrin, for each man, are related both to his exposure and to his absorption, and, further, that his absorption depends on his exposure. Provided that a man is in equilibrium with his exposure then his excretion levels of both metabolites will be constant, and if he is healthy then his condition will not deteriorate while his absorption remains constant. Different men tolerate lead differently, and the urinary excretion of metabolites depends on numerous factors. It appears that rather than compare each result with the M.U.C. it would be a more practicable method of screening the personnel to detect changes in the excretion levels. This in turn raises the problem of whether a change, which has occurred, is due to biological variation or is in fact due to a change in the hazard.

If specimens of about 4 litres of urine are taken the biological variation will be reduced to a minimum. However, the collection of these large specimens presents some difficulties when workpeople are allowed to contribute urine without supervision. Unless the personnel are of high integrity false or contaminated specimens are likely to be sent for analysis. This same objection applies equally to 24-hour urine collections. It is often more convenient to obtain a spot specimen when the man visits the medical centre.

Unfortunately, spot specimens show greater variability than any cumulative sample. Furthermore, the concentrations of metabolites tend to rise as the working day progresses. In addition, each individual has his own diurnal rhythm. So as to reduce these effects it is necessary that all specimens should be collected at a time specified in relation to the working period. Probably the best time would be at the beginning of the shift when the average excretion and hence the variability is at a minimum.

If a large number of spot specimens (about 30 to 40) are analysed during a period when the individual is in equilibrium with his environment, the biological variation can be measured. However, it was shown in Part I that the square roots of the concentrations fall in a normal distribution about the average excretion level. It is therefore possible to devise a quality control method, which, by providing estimates of the average and of the variability, will indicate statistically significant changes in the mean excretion level. The method described below was originally designed for the interpretation of spot specimens but can be applied to most screening tests.

The Theory of Quality Control as Applied to Screening Tests

Provided that the man is in equilibrium with his environment his urinary excretion levels of lead and coproporphyrin will be constant. Suppose that the averages of groups of samples ($\bar{x}_1, \bar{x}_2, \bar{x}_3, \ldots \bar{x}_k$) are plotted in order, how can it be judged whether their fluctuations about the mean level ($\bar{\bar{X}}$) are exceptional or not? Theory indicates that if the variation among the groups is uniform, $\bar{x}$ should vary about $\bar{\bar{X}}$ with a standard error of $s/\sqrt{n}$, and further that the scatter is in accordance with the Normal Law of probability. It follows that it would be expected that:

50 averages in 1000 would fall above $\bar{\bar{X}} + 1{\cdot}645\, s/\sqrt{n}$
50 averages in 1000 would fall below $\bar{\bar{X}} - 1{\cdot}645\, s/\sqrt{n}$
25 averages in 1000 would fall above $\bar{\bar{X}} + 1{\cdot}960\, s/\sqrt{n}$
25 averages in 1000 would fall below $\bar{\bar{X}} - 1{\cdot}960\, s/\sqrt{n}$
1 average in 1000 would fall above $\bar{\bar{X}} + 3{\cdot}09\, s/\sqrt{n}$
1 average in 1000 would fall below $\bar{\bar{X}} - 3{\cdot}09\, s/\sqrt{n}$

In other words,

90% limits $= \bar{\bar{X}} \pm A_{0\,050}s$
95% limits $= \bar{\bar{X}} \pm A_{0{\cdot}025}s$
99·8% limits $= \bar{\bar{X}} \pm A_{0{\cdot}001}s$

The calculation of each group average is easy but the calculation of every standard deviation is more laborious. For this reason it is the usual practice to base the estimation of the standard deviation on the group range, *i.e.*, the difference between the highest and lowest readings of any one group. Where each group contains the same number of samples the following equation can be used to estimate the standard deviation:

$$Se = \frac{1}{d_n} \cdot \frac{1}{k}(w_1 + w_2 + w_3 + \ldots w_k) = \frac{1}{d_n} \cdot \bar{W}$$

where Se is the estimated standard deviation, $\frac{1}{d_n}$ is the factor for converting the average range to the standard deviation, k is the number of groups, w is the range of each group, and $\bar{W}$ is the average range.

By using this equation a little of the available information is lost, but as each group is only a check on the mean excretion level the moderate loss is more than compensated for by the time saved in the routine calculation of the standard deviation. The two equations can be combined thus:

$$90\%\ \text{limits} = \bar{\bar{X}} \pm A_{0{\cdot}050} \cdot \frac{1}{d_n} \cdot \bar{W}$$

$$95\%\ \text{limits} = \bar{\bar{X}} \pm A_{0{\cdot}025} \cdot \frac{1}{d_n} \cdot \bar{W}$$

$$99{\cdot}8\%\ \text{limits} = \bar{\bar{X}} \pm A_{0{\cdot}001} \cdot \frac{1}{d_n} \cdot \bar{W}$$

All these constants are shown in Table IV.

TABLE IV

STATISTICAL FACTORS FOR ESTIMATING THE STANDARD DEVIATION AND LIMITS

No. of Samples in Group	$\frac{A_{0{\cdot}001}}{d_n}$	$\frac{A_{0{\cdot}025}}{d_n}$	$\frac{A_{0{\cdot}050}}{d_n}$
2	1·936	1·228	1·0307
3	1·054	0·669	0·5613
4	0·750	0·476	0·3997
5	0·594	0·377	0·3164
6	0·498	0·316	0·2648
7	0·432	0·274	0·2300
8	0·384	0·243	0·2044
9	0·347	0·220	0·1845
10	0·317	0·201	0·1689

This table has been compiled from data according to Pearson (1935), Davies (1949), and Moroney (1953).

The Control Method From the above theory a simple method has been devised. The method indicates the excretion level and the 90% confidence limits from groups of four consecutive samples. The average of four samples was chosen because the 90% limits can be estimated by multiplying the average range by 0·3997 (which for practical purposes is 4/10). In this scheme, significant changes in the level are indicated when any independent group average exceeds the limits deduced from previous groups. Since the method was designed for routine investigations the observed results are used instead of the square roots of the concentrations. The method is still applicable, however. As the limits are arranged symmetrically about the mean level more than one average in 20 would be expected to lie above the upper limit and less than one in 20 below the lower limit, although only one in 10 would fall beyond either limit. The loss in accuracy is more than offset by the time saved and by reducing the arithmetical errors which could arise. For work of higher precision the square roots of the concentrations could be used.

It is usual to collect the samples at weekly, monthly, or even longer intervals. Hence there is a long period when little information can be deduced. Since it would be wasteful to ignore each result until a complete group has been collected, the moving average (the average of the four latest results) is used to monitor the excretion level until the group is complete. If this scheme is compared with the usual technique the moving average replaces the spot result and the upper confidence limit replaces the M.U.C. Thus each man can be protected without defining a generally applicable M.U.C.

The Record Form and Chart The method consists of entering the results in a record form (Tables V and VI) and plotting a chart (Figs. 10 and 11).

TABLE V

Coproporphyrin Concentrations (μg./l.) of Urine Spot Specimens Collected from Subject A Over a Period of 24 Months

1	2	3	4	5	6	7	8	9	10	11
Date	Observed Result	Average of four results = Group average	Sum of group averages	Col. 4 divided by Group No. = Grand average	Range of four observed results = Group range	Sum of group ranges	Col. 7 divided by Group No. = Average group range	Col. 8 × 4/10 = 90% conf. limit	Col. 5 + Col. 9 = Upper limit of mean	Col. 5 − Col. 9 = Lower limit of mean
	500									
	800									
	400									
	2100									
GROUP No. 1		950	950	950	1700	1700	1700	680	1630	270
	600	975								
	800	975								
	300	950								
	300									
GROUP No. 2		500	1450	725	500	2200	1100	440	1165	285
	1600	750								
	400	650								
	400	675								
	300									
GROUP No. 3		675	2125	708	1300	3500	1167	467	1175	242
	600	425								
	400	425								
	800	525								
	700									
GROUP No. 4		625	2750	688	400	3900	975	390	1078	298
	1000	725								
	700	800								
	700	775								
	400									
GROUP No. 5		700	3450	690	600	4500	900	360	1050	330
	700	625								
GROUP No. 6										

TABLE VI

Coproporphyrin Concentrations (μg./l.) of Urine Spot Specimens Collected from Subject B Over a Period of 15 Months

1	2	3	4	5	6	7	8	9	10	11
Date	Observed Result	Average of four results = Group average	Sum of group averages	Col. 4 divided by Group No. = Grand average	Range of four observed results = Group range	Sum of group ranges	Col. 7 divided by Group No. Average group range	Col. 8 × 4/10 = 90% conf. limit	Col. 5 + Col. 9 = Upper limit of mean	Col. 5 − Col. 9 = Lower limit of mean
	200									
	200									
	200									
	200									
GROUP No. 1		200	200	200	0	0	0	0	200	200
	200	200								
	200	200								
	200	200								
	300	225								
GROUP No. 2		225	425	213	100	100	50	20	233	193
	400	275								
	300	300								
	200	300								
	700	400								
GROUP No. 3		400	825	275	500	600	200	80	355	195
REASSESS										
GROUP No. 3 BECOMES GROUP No. 1										
	400	275								
	300	300								
	200	300								
	700	400								
GROUP No. 1		400	400	400	500	500	500	200	600	200
	600	450								
	400	475								
	200	475								
	800	500								
GROUP No. 2		500	900	450	600	1100	550	220	670	230

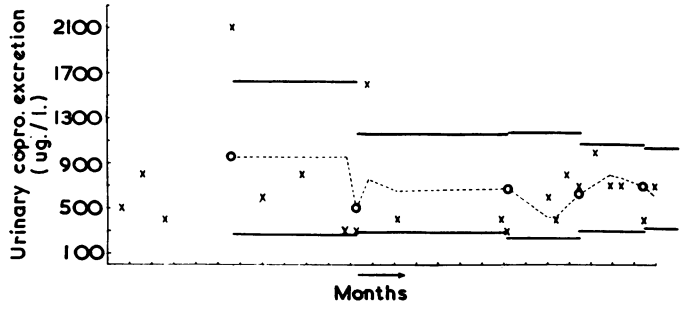

FIG. 10. The record chart of subject A: ×, observed result; ○, group mean; - - - - moving average; —— 90% confidence limits.

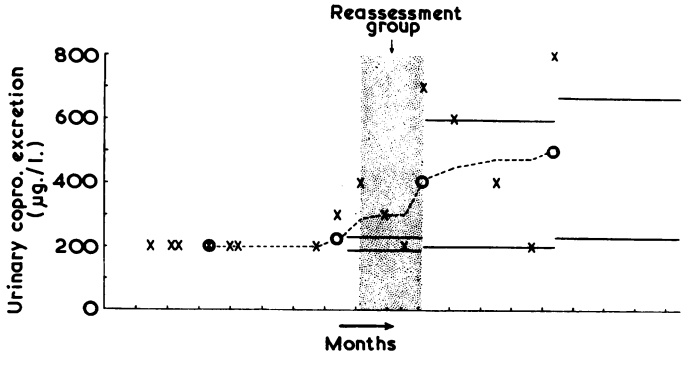

FIG. 11. The record chart of subject B: ×, observed result; ○, group mean; - - - - moving average; —— 90% confidence limits.

The record form consists of 11 columns divided into groups of four down the page. The first column is for the date which fixes the points on the ordinate of the chart. The second column shows the observed results. The moving average of four consecutive results is placed in column three. The remainder of the columns can only be used with independent groups of four results. Column 4 shows the sum of the independent group averages which, when divided by the number of groups, gives the grand average of all the observed results, and this is placed in column 5. The next four columns are used to calculate the 90% confidence limits. Column 6 shows the range (the difference between the highest and the lowest in the group). Column 7 shows the sum of the ranges which when divided by the number of groups gives the average range. This is placed in column 8. In column 9, the average range is multiplied by 4/10 to convert the average range to 90% confidence limit. Column 10 gives the grand mean (column 5) plus the limit value, and column 11 gives the grand mean minus the limit value, thus giving the upper and lower confidence limits.

Interpretation of the Record Form and Chart

Figures 10 and 11 were derived from the data in Tables V and VI which were obtained from an anonymous firm. The charts were plotted from the values in columns 1, 3, 10, and 11. The moving average is shown as a broken line. The open circles are the independent group averages, and the horizontal full lines are the confidence limits. In these figures the spot results, shown as 'Xs', have been included for comparison.* In Fig. 10 are shown the results of one man. As the results were obtained and the chart built up it was seen that his excretion level remained constant. The precision of both the grand mean and the limits increased as more data were collected.

It will be noted that although this man appears to be excreting an exorbitant quantity of coproporphyrins, he was healthy throughout this period (haemoglobin never below 14·7 g./100 ml.). However, he was working under adverse conditions and usually passed small volumes of concentrated urine.

Figure 11 shows the results of a man with an excretion level stable for eight months followed by a rise over the remaining period. The spot results (shown as 'Xs') are difficult to interpret but the moving average (the broken line) demonstrates a continual upward trend. In Table VI the upper limit

* It must be remembered that the confidence limits apply only to *means* of 4; individual spot specimen results will often fall outside these limits, without signifying a change in the man's excretion level.

of the first two groups (column 10) is exceeded by the first and subsequent moving averages of the third group. If this scheme had been in operation at the time, the samples to complete the group would have been collected at shorter intervals. Although the observed results ('Xs') point to a return to the low level, the third group average is significantly higher than the previous averages. This result could have been a chance observation but it is essential to consider each rise above the limit as being due to some ascribable reason before attributing it to chance. In fact the man had moved to a different department and was found to be healthy so he was allowed to remain at the new job. Since the man has a higher excretion level the results of the first two groups cannot be used with the latter values, so a new series begins. This notion of discarding all the results of a previous stable period must be adopted since the scatter and hence the limits depend on the excretion level (see Part I). If this is not done, when the level rises the limits will be too close together; conversely, when the level falls the limits will be too wide apart. This will make it more difficult to detect changes in the excretion levels.

Provided a standard procedure is adopted for the collection of the urine and the manner in which the results are expressed, this scheme will indicate significant changes in the excretion levels. Considerable care is needed in the interpretation of the data. It is possible to detect a significant fall in the metabolite concentration yet the man may be exposed to a greater hazard. One circumstance in which this paradoxical situation could arise is when a man, who has been in equilibrium with an extremely hot thermal environment at low risk and is then transferred to a normal environment at a higher risk, has specimens collected towards the end of the shift. It is apparent that some more reliable guide to the lead absorption must be measured, as well as having the man clinically examined, whenever a significant change in the metabolite level is detected and whenever the man changes his job.

The author is indebted to Professor R. C. Browne for permission to publish this paper; to Dr. J. Steel for general supervision of the work and many stimulating discussions; to Dr. R. I. McCallum for providing the subjects; to Dr. D. J. Newell for statistical advice; to Mrs. D. Weightman for preparing the diagrams; and to Mrs. M. Bell and Miss S. Lowes for technical assistance.

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APPENDIX

TABLE AI

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT C

Specimen	*Time of Collection*	*Hours Between Voidings*	*Volume (ml.)*	*Lead (μg.)*			*Coproporphyrin (μg.)*			*Creatinine (g.)*		*Specific Gravity*
				Litre	*Specimen*	*Hour*	*Litre*	*Specimen*	*Hour*	*Litre*	*Specimen*	
1	1.30 p.m.	—	532	33	17	—	174	93	—	0·539	0·287	1·005
2	5.00	3·50	405	49	19	5·43	315	128	36·6	0·884	0·358	1·009
3	9.15	4·25	259	98	26	6·12	467	121	28·5	1·485	0·385	1·014
4	10.15	1·00	80	44	4	4·00	492	40	10·0	1·332	0·107	1·013
5	6.15 a.m.	8·00	223	38	8	1·00	962	214	26·8	2·182	0·487	1·013
6	11.15	5·00	419	30	13	2·60	292	123	24·6	0·664	0·278	1·007
7	1.30 p.m.	2·25	200	71	14	6·22	575	115	51·1	0·950	0·190	1·012
8	5.45	4·25	383	65	25	5·88	509	195	45·9	0·971	0·372	1·009
9	10.00	4·25	358	69	25	5·88	430	154	36·2	1·075	0·385	1·012
10	6.45 a.m.	8·75	230	76	17	1·94	974	176	20·1	3·684	0·847	1·016
11	9.00	2·25	230	20	5	2·22	307	71	31·6	0·502	0·115	1·004
12	10.45	1·75	325	34	11	6·29	201	68	38·9	0·867	0·282	1·006
13	1.00 p.m.	2·25	260	48	12	5·33	328	85	37·8	0·788	0·205	1·008
Total		47·5	3,904		196			1,583			4·296	
'Mean'				50·2		3·77	405·5		31·37	1·100		

TABLE AII

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT K

Specimen	*Time of Collection*	*Hours Between Voidings*	*Volume (ml.)*	*Lead (μg.)*			*Coproporphyrin (μg.)*			*Creatinine (g.)*		*Specific Gravity*
				Litre	*Specimen*	*Hour*	*Litre*	*Specimen*	*Hour*	*Litre*	*Specimen*	
1	1.00 p.m.	—	92	61	6	—	605	57	—	1·541	0·142	1·024
2	4.00	3·00	87	84	7	2·33	353	31	10·3	0·932	0·080	1·018
3	7.15	3·25	390	72	28	8·60	139	55	16·9	0·340	0·134	1·008
4	10.15 a.m.	15·00	75	93	7	0·47	1,090	72	4·8	—	—	1·025
5	1.15 p.m.	3·00	124	55	7	2·33	671	83	27·7	0·995	0·124	1·027
6	3.45	2·50	223	114	25	10·00	529	118	42·9	0·900	0·201	1·023
7	5.45	2·00	185	81	15	7·50	253	47	23·5	0·850	0·157	1·020
8	8.30	2·75	193	43	8	2·90	549	106	38·5	0·916	0·177	1·027
9	10.30	2·00	90	43	4	2·00	405	37	18·5	1·387	0·125	1·028
10	6.00 a.m.	7·50	180	169	30	4·00	511	92	12·3	1·181	0·212	1·022
11	9.15	3·25	133	145	19	5·80	643	86	26·5	1·550	0·206	1·025
12	1.30 p.m.	4·25	185	60	11	2·60	424	79	18·6	0·770	0·238	1·022
13	4.00	2·50	425	86	37	14·80	290	123	49·2	0·420	0·179	1·015
14	6.00	2·00	271	61	17	8·50	219	59	29·5	0·580	0·157	1·014
15	9.30	3·50	120	53	6	1·67	726	87	24·9	1·144	0·137	1·026
16	12.15 a.m.	2·75	242	48	12	4·40	432	105	38·2	1·005	0·243	1·023
17	4.45	4·50	290	84	24	5·30	620	180	40·0	1·181	0·342	1·025
Total		63·75	3,305		263			1,417			2·854	
'Mean'				79·6		4·03	429		21·33	0·884		

TABLE AIII

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT N

Specimen	*Time of Collection*	*Hours Between Voidings*	*Volume (ml.)*	*Lead (μg.)*			*Coproporphyrin (μg.)*			*Creatinine (g.)*		*Specific Gravity*
				Litre	*Specimen*	*Hour*	*Litre*	*Specimen*	*Hour*	*Litre*	*Specimen*	
1	2.00 p.m.	—	60	354	25	—	1,164	72	—	1·194	0·072	1·028
2	7.15	5·25	273	437	119	22·7	814	222	42·3	0·762	0·208	1·023
3	10.30	3·25	233	292	68	20·9	504	118	36·3	1·205	0·281	1·019
4	6.00 a.m.	7·50	286	177	51	6·8	687	197	26·3	—	—	1·018
5	8.30	2·50	98	214	22	8·8	937	92	36·9	1·134	0·111	1·020
6	10.15	1·75	260	166	35	20·0	265	69	39·4	—	—	1·009
7	1.00 p.m.	2·25	355	134	48	21·3	374	133	59·1	—	—	1·009
8	3·45	2·75	515	70	36	13·1	324	167	60·7	0·286	0·147	1·007
9	7.30	3·75	315	196	63	16·8	442	139	50·5	0·430	0·135	1·012
10	10.45	3·25	184	319	59	18·2	758	140	43·1	0·645	0·119	1·020
11	5.45 a.m.	7·00	181	371	67	9·6	846	153	21·9	0·838	0·152	—
12	9.30	3·75	116	363	42	11·2	1,445	168	44·8	0·352	0·041	1·024
13	11.15	1·75	200	127	26	14·9	354	71	40·6	0·855	0·171	1·007
14	1.00 p.m.	1·75	123	329	40	22·9	1,031	127	72·6	0·606	0·074	1·015
15	4.00	3·00	542	162	88	29·3	312	170	56·7	1·469	0·796	—
16	6.30	2·50	158	345	55	22·0	713	113	45·2	1·246	0·197	1·020
17	9.00	2·50	131	460	60	24·0	796	104	41·6	1·283	0·168	1·022
18	10.45	1·75	70	361	26	14·9	1,010	71	40·6	0·364	0·025	—
19	4.30 a.m.	5·75	545	140	76	13·2	278	152	26·4	0·838	0·457	1·012
20	10.15	5·75	234	151	36	6·3	480	112	19·5	0·867	0·203	1·010
21	12.45 p.m.	2·50	133	279	37	14·8	506	67	26·8	0·645	0·086	1·017
Total		70·25	5,021		1,079			2,657			3·443	
'Mean'				214		15·00	529		36·80	0·836		

TABLE AIV

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT P

Specimen	*Time of Collection*	*Hours Between Voidings*	*Volume (ml.)*	*Lead (μg.)*			*Coproporphyrin (μg.)*			*Creatinine (g.)*		*Specific Gravity*
				Litre	*Specimen*	*Hour*	*Litre*	*Specimen*	*Hour*	*Litre*	*Specimen*	
1	9.50 a.m.	—	316	350	111	—	518	182	—	0·813	0·257	1·014
2	1.00 p.m.	3·16	366	460	168	53	385	141	45	0·421	0·154	1·011
3	6.30	5·50	250	470	118	22	528	132	24	0·898	0·225	1·019
4	9.15	2·75	231	498	115	42	610	141	51	0·789	0·245	1·019
5	3.15 a.m.	6·00	318	238	76	13	627	199	33	1·098	0·349	1·013
6	11.00	7·75	281	324	91	10	750	211	24	0·947	0·266	1·013
7	2.20 p.m.	3·33	283	369	104	31	743	201	60	0·622	0·176	1·015
8	5.50	3·50	363	394	143	41	543	197	56	0·600	0·218	1·013
9	10.25	4·58	201	593	119	26	655	132	29	0·943	0·190	1·021
10	11.30	1·08	276	117	32	28	178	49	45	0·285	0·079	1·006
11	4.30 a.m.	5·00	344	207	71	13	541	186	34	0·789	0·275	1·013
12	12 noon	7·50	363	333	121	16	591	215	29	0·745	0·270	1·011
13	2.30 p.m.	2·50	258	266	67	27	474	122	49	0·706	0·182	1·012
14	5.50	3·33	175	371	65	17	609	107	28	0·956	0·167	1·018
15	9.50	4·00	276	451	125	31	566	156	39	0·887	0·245	1·018
16	5.00 a.m.	7·16	538	291	157	22	592	318	44	1·094	0·588	1·016
17	9.30	4·50	44	402	17	4	1,482	65	14	2·360	0·104	1·021
Total		71·67	4,883		1,700			2,754			3·990	
'Mean'				350		22·6	563		35·9	0·8171		

TABLE AV

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT P2

Specimen	Time of Collection	Hours Between Voidings	Volume (ml.)	Lead (μg.)			Coproporphyrin (μg.)			Creatinine (g.)		Specific Gravity
				Litre	Specimen	Hour	Litre	Specimen	Hour	Litre	Specimen	
1	9.00 a.m.	—	265	165	44	—	45	12	—	0·806	0·214	1·013
2	12 noon	3·00	345	88	30	10·00	72	25	8·33	0·303	0·105	1·004
3	4.00 p.m.	4·00	415	37	15	3·75	144	60	15·00	0·542	0·225	1·015
4	8.45	4·75	390	150	59	12·40	88	34	7·16	0·797	0·311	1·016
5	11.30	2·75	280	98	27	9·80	85	24	8·73	0·844	0·235	1·019
6	5.00 a.m.	5·50	450	98	44	8·00	107	48	8·73	1·033	0·465	1·020
7	11.30	6·50	485	100	49	7·50	44	21	3·23	0·371	0·180	1·008
8	4.00 p.m.	4·50	335	106	36	8·00	57	17	3·78	0·585	0·200	1·011
9	8.00	4·00	585	52	30	7·50	47	28	7·00	1·014	0·593	1·018
10	9.00 a.m.	13·00	430	88	38	3·50	18	8	0·73	0·255	0·120	1·007
11	1.00 p.m.	4·00	405	115	47	11·80	78	32	8·00	1·019	0·413	1·020
12	6.00	5·00	475	87	41	8·20	3	2	0·40	0·753	0·358	1·017
13	11.30	5·50	325	53	17	3·10	6	2	3·60	0·533	0·173	1·011
14	12 noon	12·50	370	45	17	2·60	42	16	1·28	0·258	0·095	1·006
15	2.25 p.m.	2·42	375	75	28	11·60	47	18	7·44	0·346	0·130	1·004
16	7·00	4·58	380	76	29	6·40	92	35	7·64	0·700	0·266	1·016
17	5.30 a.m.	10·50	570	80	46	4·40	83	47	4·48	0·775	0·442	1·018
Total		92·50	6,880		597			429			4·525	
'Mean'				86·77		6·45	62·4		5·34	0·658		

TABLE AVI

OBSERVED RESULTS FROM SPOT URINE SPECIMENS: PATIENT U

Specimen	Time of Collection	Hours Between Voidings	Volume (ml.)	Lead (μg.)			Coproporphyrin (μg.)			Creatinine (g.)		Specific Gravity
				Litre	Specimen	Hour	Litre	Specimen	Hour	Litre	Specimen	
1	3.40 p.m.	—	310	51	16	—	95	30	—	0·679	0·211	1·008
2	9.30	5·83	320	84	27	4·63	74	25	4·29	0·766	0·245	1·014
3	12.20 a.m.	2·83	340	50	17	6·00	98	35	12·37	0·434	0·148	1·012
4	4.40	4·33	420	35	15	3·46	65	28	6·47	0·587	0·247	1·010
5	6.25	1·75	188	41	8	4·57	121	23	13·14	0·744	0·140	1·012
6	9.25	3·00	215	25	5	1·67	124	28	9·33	1·031	0·220	1·009
7	11.20	1·92	229	38	9	4·69	105	25	13·02	0·628	0·144	1·007
8	3.45 p.m.	4·43	450	48	22	4·63	205	93	19·58	0·587	0·265	1·008
9	5.35	1·83	340	50	17	9·29	127	43	23·50	0·392	0·133	1·006
10	8.00	2·42	320	30	10	4·13	118	38	15·70	0·514	0·164	1·005
11	11.15	3·25	355	45	16	4·92	123	44	13·54	0·448	0·159	1·006
12	3.45 a.m.	4·50	410	27	11	2·44	111	46	10·22	—	—	—
13	5.45	2·00	345	51	18	9·00	149	52	26·00	0·539	0·186	1·006
14	10.05	4·33	195	76	15	3·46	540	105	24·25	1·471	0·287	1·012
15	12.20 p.m.	2·25	260	40	10	4·44	199	52	23·11	0·420	0·109	1·009
16	2.50	2·50	215	30	6	2·40	122	26	10·40	0·425	0·091	1·007
17	4.55	2·08	176	55	14	6·73	173	31	14·90	0·643	0·113	1·012
18	7.10	2·25	240	35	14	6·22	172	41	18·22	0·589	0·141	1·010
19	10.10	3·00	402	43	14	4·66	137	55	18·33	0·715	0·287	1·010
20	5.20 a.m.	7·17	320	50	11	1·53	171	55	7·67	0·790	0·253	1·010
21	7.15	1·83	205	31	7	3·83	226	47	25·68	0·776	0·159	1·008
Total		63·50	6,255		282			922			3·702	
'Mean'				45·1		4·44	147·4		14·03	0·633		

TABLE AVII

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT C

Specimen	*Time*	*Lead*				*Coproporphyrin*				*Creatinine* (% concentration[3])	*Specific Gravity*
		% Concentration[1]	*% Rate/hour*[2]	*Concentration adjusted to*		*% Concentration*[1]	*% Rate/hour*[2]	*Concentration adjusted to*			
				Specific Gravity	*Creatinine*			*Specific Gravity*	*Creatinine*		
1	1.30 p.m.	66	—	198	135	43	—	131	89	49	1·005
2	5.00	98	204	164	121	78	117	130	96	80	1·009
3	9.15	195	164	211	145	116	91	125	85	135	1·014
4	10.15	88	107	102	72	121	32	142	100	121	1·013
5	6.15 a.m.	76	27	89	38	237	85	276	119	199	1·013
6	11.15	60	70	103	100	72	78	155	119	60	1·007
7	1.30 p.m.	141	170	179	163	142	163	179	163	86	1·012
8	5.45	129	159	217	145	126	146	212	142	88	1·009
9	10.00	137	159	173	140	106	116	133	107	98	1·012
10	6.45 a.m.	151	52	143	45	240	64	227	72	335	1·016
11	9.00	40	60	152	88	76	101	288	167	46	1·004
12	10.45	68	169	171	85	50	124	131	65	79	1·006
13	1.00 p.m.	96	143	180	132	81	120	152	112	72	1·008
Average		103·5	123·7	160·2	108·4	114·5	103·1	175·5	110·5		
n		13	12	13	13	13	12	13	13		

TABLE AVIII

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT K

Specimen	*Time*	*Lead*				*Coproporphyrin*				*Creatinine* (% concentration[3])	*Specific Gravity*
		% Concentration[1]	*% Rate/hour*[2]	*Concentration Adjusted to*		*% Concentration*[1]	*% Rate/hour*[2]	*Concentration Adjusted to*			
				Specific Gravity	*Creatinine*			*Specific Gravity*	*Creatinine*		
1	1.00 p.m.	76	—	51	43	141	—	89	79	178	1·024
2	4.00	104	58	93	97	82	48	69	77	107	1·018
3	7.15	88	213	178	226	32	79	62	82	39	1·008
4	10.15 a.m.	114	12	74	—	254	23	154	—	—	1·025
5	1.15 p.m.	68	58	41	59	156	130	88	136	115	1·027
6	3.45	140	248	97	135	123	201	81	118	104	1·023
7	5.45	100	186	80	102	59	110	45	60	98	1·020
8	8.30	53	72	31	50	128	181	72	121	106	1·027
9	10.30	53	50	31	33	94	87	51	59	160	1·028
10	6.00 a.m.	208	99	152	152	119	58	82	87	137	1·022
11	9.15	179	144	114	100	150	124	91	84	179	1·025
12	1.30 p.m.	74	64	54	82	99	87	68	111	89	1·022
13	4.00	106	367	121	216	68	231	68	139	49	1·015
14	6.00	76	211	86	113	51	138	55	76	67	1·014
15	9.30	66	41	41	50	169	117	98	128	132	1·026
16	12.15 a.m.	59	109	41	51	101	179	67	87	116	1·023
17	4.45	104	131	67	76	144	188	87	105	137	1·025
Average		98·1	128·9	79·5	99·1	115·9	123·8	78·1	96·8		
n		17	16	17	16	17	16	17	16		

[1]Working units μg./litre; weighted 'mean' concentration = 100%.
[2]Working units μg./hour; weighted 'mean' rate = 100%.
[3]Working units g./litre; weighted 'mean' concentration = 100%.

TABLE AIX

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT N

Specimen	Time	Lead				Coproporphyrin				Creatinine (% concentration[3])	Specific Gravity
		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to			
				Specific Gravity	Creatinine			Specific Gravity	Creatinine		
1	2.00 p.m.	165	—	94	115	220	—	126	154	143	1·028
2	7.15	204	153	142	224	154	116	107	169	91	1·023
3	10.30	136	141	115	94	95	99	80	66	144	1·019
4	6.00 a.m.	83	46	74	—	130	72	116	—	—	1·018
5	8.30	100	59	80	74	177	101	142	131	135	1·020
6	10.15	78	135	139	—	50	108	89	—	—	1·009
7	1.00 p.m.	63	144	112	—	71	162	126	—	—	1·009
8	3.45	33	88	75	97	61	166	139	179	34	1·007
9	7.30	92	113	123	180	84	138	112	165	51	1·012
10	10.45	149	123	119	194	143	118	114	186	77	1·020
11	5.45 a.m.	173	65	—	173	160	60	—	160	100	—
12	9.30	170	75	113	405	273	123	182	650	42	1·024
13	11.15	59	100	135	58	67	111	153	66	102	1·007
14	1.00 p.m.	154	154	164	214	195	199	208	270	72	1·015
15	4.00	76	197	—	44	59	155	—	34	175	—
16	6.30	161	148	129	108	135	124	108	91	149	1·020
17	9.00	215	162	156	141	150	114	109	98	153	1·022
18	10.45	169	100	—	393	190	111	—	441	43	—
19	4.30 a.m.	65	89	87	65	53	72	71	53	100	1·012
20	10.15	71	42	114	68	91	53	146	88	104	1·010
21	12.45 p.m.	130	100	122	169	96	73	90	125	77	1·017
Average		121·2	111·7	116·3	156·4	126·4	113·8	123·2	173·7		
n		21	20	18	18	21	20	18	18		

TABLE AX

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT P

Specimen	Time	Lead				Coproporphyrin				Creatinine (% concentration[3])	Specific Gravity
		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to			
				Specific Gravity	Creatinine			Specific Gravity	Creatinine		
1	9.50 a.m.	100	—	114	101	92	—	105	93	99	1·014
2	1.00 p.m.	131	239	191	252	68	126	99	131	52	1·011
3	6.30	134	99	113	122	94	67	79	85	110	1·019
4	9.15	142	189	120	146	108	142	91	111	97	1·019
5	3.15 a.m.	68	59	83	51	111	92	137	83	134	1·013
6	11.00	93	45	114	80	133	67	164	115	116	1·013
7	2.20 p.m.	105	140	112	138	132	167	141	173	76	1·015
8	5.50	113	185	139	155	96	156	118	132	73	1·013
9	10.25	169	117	129	150	116	81	89	113	113	1·021
10	11.30	33	126	89	94	32	126	84	91	35	1·006
11	4.30 a.m.	59	59	73	60	96	95	118	98	98	1·013
12	12 noon	95	72	139	104	105	81	153	115	91	1·011
13	2.30 p.m.	76	121	101	88	84	137	112	98	86	1·012
14	5.50	106	77	94	91	108	78	96	92	117	1·018
15	9.50	129	140	115	118	101	109	89	93	109	1·018
16	5.00 a.m.	83	99	83	62	105	123	105	78	134	1·016
17	9.30	115	18	87	40	263	39	201	91	289	1·021
Average		103·0	111·6	111·5	108·9	108·5	105·4	116·5	105·4		
n		17	16	17	17	17	16	17	17		

[1]Working units μg./litre; weighted 'mean' concentration = 100%.
[2]Working units μg./hour; weighted 'mean' rate = 100%.
[3]Working units g./litre; weighted 'mean' concentration = 100%.

TABLE AXI

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT P2

Specimen	Time	Lead				Coproporphyrin				Creatinine (% concentration[3])	Specific Gravity
		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to			
				Specific Gravity	Creatinine			Specific Gravity	Creatinine		
1	9.00 a.m.	192	—	236	156	76	—	94	61	123	1·013
2	12 noon	102	155	408	221	122	180	488	265	46	1·004
3	4.00 p.m.	43	58	46	52	244	323	260	293	83	1·015
4	8.45	174	192	174	143	149	154	149	122	122	1·016
5	11.30	114	152	96	82	144	188	121	112	129	1·019
6	5.00 a.m.	114	124	91	72	181	188	145	115	158	1·020
7	11.30	116	116	232	204	75	70	150	132	57	1·008
8	4.00 p.m.	123	124	179	138	86	81	125	97	89	1·011
9	8.00	60	116	53	39	80	151	71	51	155	1·018
10	9.00 a.m.	102	54	233	262	31	16	71	79	39	1·007
11	1.00 p.m.	134	183	107	86	132	172	106	85	156	1·020
12	6.00	107	127	101	93	5	9	5	4	115	1·017
13	11.30	62	48	90	77	10	78	15	12	81	1·011
14	12 noon	52	40	139	133	71	28	189	182	39	1·006
15	2.45 p.m.	87	180	348	164	80	160	320	151	53	1·004
16	7.00	88	99	88	82	156	165	156	146	107	1·016
17	5.30 a.m.	93	68	83	79	141	97	125	119	118	1·018
Average		103·7	114·8	159·1	122·5	104·9	128·8	152·4	119·2		
n		17	16	17	17	17	16	17	17		

TABLE AXII

PROPORTIONS OF 'MEAN' EXCRETION: PATIENT U

Specimen	Time	Lead				Coproporphyrin				Creatinine (% concentration[3])	Specific Gravity
		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to		% Concentration[1]	% Rate/hour[2]	Concentration adjusted to			
				Specific Gravity	Creatinine			Specific Gravity	Creatinine		
1	3.40 p.m.	113	—	226	106	61	—	122	57	107	1·008
2	9.30	186	104	213	154	48	27	55	40	121	1·014
3	12.20 a.m.	111	135	148	161	63	77	84	91	69	1·012
4	4.40	78	78	125	84	42	41	67	45	93	1·010
5	6.25	91	103	121	77	78	82	104	66	118	1·012
6	9.25	55	38	98	33	80	58	142	49	163	1·009
7	11.20	84	106	192	85	68	82	155	69	99	1·007
8	3.45 p.m.	106	104	212	114	132	123	264	142	93	1·008
9	5.35	111	209	296	179	82	147	219	132	62	1·006
10	8.00	67	93	214	83	76	98	243	94	81	1·005
11	11.15	100	111	267	141	79	85	211	111	71	1·006
12	3.45 a.m.	60	55	—	—	72	64	—	—	—	—
13	5.45	113	203	301	133	96	163	256	113	85	1·006
14	10.05	169	78	225	73	348	152	464	150	232	1·012
15	12.20 p.m.	89	100	158	135	128	145	228	194	66	1·009
16	2.50	67	54	153	100	79	65	181	118	67	1·007
17	4.55	122	151	163	121	112	93	149	111	101	1·012
18	7.10	78	140	125	84	111	114	178	119	93	1·010
19	10.10	95	105	152	84	88	115	141	78	113	1·010
20	5.20 a.m.	111	34	178	89	110	48	176	88	125	1·010
21	7.15	69	86	138	56	146	161	292	119	123	1·008
Average		98·8	104·4	185·3	104·6	100	97	186·6	99·8		
n		21	20	20	20	21	20	20	20		

[1]Working units μg./litre; weighted 'mean' concentration = 100%.
[2]Working units μg./hour; weighted 'mean' rate = 100%.
[3]Working units g./litre; weighted 'mean' concentration = 100%.