KINETICS OF RESPIRATORY LEAD UPTAKE IN HUMANS

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ZUSAMMENFASSUNG

Aus Untersuchungen über die biologischen Wirkungen einer längere Zeit dauernden Belastung des Menschen durch bleihaltige Luft wurden die Daten beschafft, die zur Ausarbeitung eines mathematischen Modells für die Kinetik der Bleiaufnahme mit der Atemluft bei Menschen benötigt wurden. Männliche erwachsene Versuchspersonen waren zweimal für 18 Wochen mittleren Bleiexpositionen von einmal $10{,}9 \pm 3{,}1\ \mu g/m^3$ *und zum anderen* $3{,}2 \pm 0{,}6\ \mu g/m^3$ *ausgesetzt.*

Die Bleikonzentrationen in der Luft wurden mindestens zweimal täglich aufgezeichnet. Die Bleikonzentrationen im Blut wurden wöchentlich oder alle zwei Wochen bestimmt. Die Veränderungen im Blutbleispiegel während der Exposition wurden mit dem durchschnittlichen Blutbleigehalt vor der Exposition verglichen; daraus wurde für die Probanden die durchschnittliche Zunahme des Blutbleigehalts während jeder der beiden Versuchsabschnitte errechnet. Die potentielle Zunahme der Bleilast des Körpers wird in Abhängigkeit von Expositionsgrad, Expositionsdauer, Lungenventilation und prozentualer Retention des eingeatmeten Bleis geschätzt. Wir fanden, daß die Zunahmen in der Gesamtmenge des Blutbleis, wie sie bei beiden Expositionsniveaus beobachtet wurden, eng mit dem Logarithmus des potentiellen Körperbelastung zusammenhängen. Anhand dieser Feststellungen wurde ein mathematisches Modell entwickelt, das es ermöglicht, die wahrscheinliche Veränderung in der Blutbleikonzentration wie auch das Verhältnis zwischen dem gesamten Blutblei und der potentiellen Zunahme der Körperbelastung entsprechend den jeweiligen Expositionsbedingungen zu berechnen. Aus diesem Verhältnis läßt sich die Verteilung zwischen den beiden theoretischen Bereichen mit raschem und langsamen Umsatz ableiten.

Die einleuchtendsten Hypothesen in bezug auf Ventilation und Retention laufen darauf hinaus, daß etwa 90 % der potentiellen Gesamtkörperbelastung auf den langsamen Bereich entfallen. Wesentliche Erhöhungen des Blutbleis werden schon für solche inhalierten Bleimengen vorausgesagt, die erheblich unter denen liegen, wie sie gewöhnlich in der Außenluft vorgefunden werden.

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SUMMARY

Studies of the biological effects of long-term human exposure to airborne lead produced the data used to prepare a mathematical model of kinetics of respiratory lead uptake. Adult male subjects were subjected to two 18 week exposures at lead mean concentrations of $10.9 \pm 3.1\ \mu g/m^3$ *and of* $3.2 \pm 0.6\ \mu g/m^3$.

Air lead levels in the room were recorded at least twice daily. Blood lead levels were determined every week or every two weeks. Changes in blood lead during exposure were compared to the mean blood lead before exposure to calculate mean increase in blood lead for the subjects through both studies. Potential increase in body burden is computed as a function of exposure level, duration of exposure, pulmonary ventilation, and percent retention of inhaled lead. Blood lead concentrations multiplied by total blood volume allow one to estimate the fraction of potential body burden appearing in blood. We found that increases in total blood lead observed at the two levels of exposure were closely related to the logarithm of potential body burden. A mathematical model was developed which enables one to compute the relationship between total blood lead and potential increase in body burden. From this relationship, distribution between two theoretical compartments with rapid and slow turnover can be inferred.

The most reasonable assumptions concerning ventilation and retention indicate that about 90% of the total potential body burden goes into a slow compartment. Substantial increases in blood lead are predicted even for respiratory doses well below those commonly encountered in ambient air.

RÉSUMÉ

Des études des effets biologiques exercés sur l'homme par une exposition de longue durée au plomb atmosphérique ont permis d'obtenir les données utilisées pour élaborer un modèle mathématique de la cinétique de l'absorption respiratoire de plomb. Des adultes de sexe masculin ont été soumis à deux expositions de 18 semaines chacune à des concentrations moyennes en plomb de $10,9 \pm 3,1\ \mu g/m^3$ *dans le premier cas et de* $3,2 \pm 6\ \mu g/m^3$ *dans le second.*

Les niveaux de plomb atmosphérique présent dans la pièce ont été enregistrés au moins deux fois par jour. Les niveaux de plomb sanguin ont été déterminés toutes les semaines ou deux. Pour chacune des études on a établi une comparaison entre les changements intervenus dans le plomb sanguin au cours de l'expérience et le taux moyen de plomb sanguin avant l'expérience, pour chacun des sujets. On a calculé l'augmentation potentielle de la charge du corps comme fonction du niveau de l'exposition, de sa durée, de la ventilation pulmonaire et de la rétention de plomb exprimée en pourcentage du plomb inhalé. On a trouvé que les augmentations de plomb total dans le sang enregistrées aux deux niveaux d'exposition correspondent pratiquement au logarithme de la charge potentielle du corps. On a élaboré un modèle mathématique qui permet de calculer la relation existant entre le plomb total contenu dans le sang et l'accroissement potentiel de la charge du corps. Sur la base de cette relation, il est possible de calculer la distribution entre deux compartiments théoriques à totalisation rapide et lente des résultats. En général, les résultats obtenus à partir du modèle correspondent remarquablement bien aux résultats obtenus par d'autres chercheurs à partir de données très différentes. En ce qui concerne la ventilation et la rétention, les hypothèses les plus raisonnables indiquent que 90% environ de la charge potentielle totale du corps entrent dans un compartiment lent. On pense que même des doses respiratoires nettement inférieures à celles que l'on rencontre généralement dans l'air ambiant peuvent provoquer un accroissement considérable du taux de plomb sanguin.

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1 — INTRODUCTION

Toxic properties of lead have been recognized since antiquity. Modern industrial use of lead and compounds containing lead has, however, made human exposure to amounts of lead exceeding the normal "background level" almost universal. In particular, since introduction of tetraethyl lead as a motor fuel additive about fifty years ago, there has been a widespread dissemination of lead particles of respirable size into the atmosphere. Goldsmith and Hexter have argued that absorption of lead from respiratory exposure may be similar in magnitude to that from gastrointestinal absorption [1].

Apart from the pioneering work of Kehoe and Cholak, there is a paucity of data relating the body burden of lead to gastrointestinal or respiratory exposure levels. A large amount of information has become available relating human blood levels to ambient air lead levels in urban and rural areas, but some controversy exists concerning the interpretation of these data. Most recently, prolonged exposures of men to carefully controlled levels of lead in the air have been performed. Although a great deal of information concerning biological effects resulted from these studies, only the data related to kinetics of lead uptake from respiratory exposure are considered in this report.

2 — EXPERIMENTAL DESIGN

These studies were conducted under the direction of Drs. Frederick Coulston, Leon Golberg, and Travis Griffin in cooperation with the State of New York Department of Correctional Services at the Clinton Correction Facility, Dannemora, New York.

The subjects were carefully selected to exclude anyone with an acute or chronic disease. Baseline blood lead values were determined for several days before the controlled exposure began. The fourteen men finally selected for the study inhabited the exposure room nearly 23 hours a day, seven days a week for a total exposure duration as long as 18 weeks for many of the men. Although the subjects were encouraged to participate in the study for the entire period, no coercion was exercised and some elected to leave before the exposure ended. In order to create as large a data base as possible with the space limitations of the exposure room, other men were entered into the study already in progress.

Lead oxide aerosol was generated by bubbling propane through a solution of tetraethyl lead in dodecane and burning the resultant vapor in a highly oxidizing flame. The combustion products, almost entirely lead oxides, were introduced into the separate air conditioning system for the exposure room. Temperature and humidity control for comfort was maintained and an electrostatic precipitator removed all particulate matter from incoming outside air.

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Lead in the room air was monitored through sampling ports located at various sites in the room and analyses performed four times daily. The samples were split for immediate analysis by a colorimetric method and subsequent analysis by atomic absorption spectrophotometry. Particle size was estimated using a modified Andersen cascade sampler as well as by electron microscopy. Well over 80% of the particles had a mass median diameter of 0.18 micron or less. Most of the particles seen on the electron microscope grid were between 0.05 and 0.10 micron in diameter. Electron diffraction analysis indicated a major fraction of the particulate material was composed of αPbO_2 with traces of $Pb_3C_2O_7$, Pb(OH)Cl, and $PbCl_2$ also present. Two exposure studies were conducted. The first resulted in a mean air lead concentration of 10.9 ($\pm$3.1) $\mu g/m^3$, measured as elemental lead. The second resulted in a mean exposure of 3.2 ($\pm$0.67) $\mu g/m^3$. Blood samples were drawn in lead-free Vacutainers and blood lead concentration determined by atomic absorption spectrophotometry according to the method of Hessel [2].

3 — MATHEMATICAL METHODS

Mathematical procedures used in this initial data analysis were selected for their relative simplicity and because they could be programmed on a small computer. Preliminary results of much more detailed and complex mathematical modeling now in progress support the general conclusions of the simpler model presented here.

Potential daily intake of lead by inhalation is calculated by multiplying the mean air lead concentration each day by pulmonary ventilation. Potential daily increase in body burden is calculated by multiplying potential daily intake by the fraction of inhaled lead assumed to be retained. Total blood lead content is calculated by multiplying blood lead concentration by total blood volume. Cumulative potential increase in body burden was calculated for each interval for which blood lead determinations were available. Mean increases in total blood lead content were plotted against mean potential increases in body burden for the same exposure interval. These plots relate total blood lead content to potential increase in body burden at a given daily rate of respiratory intake of lead.

When increase in blood lead content is plotted against the logarithm of potential increase in body burden, a good linear relationship results. Therefore increase in blood lead concentration or content can be reasonably well predicted for any respiratory exposure at a given level of pulmonary ventilation and percentage retention.

4 — RESULTS AND CONCLUSIONS

The following abbreviations will be used:

IBL (μg/100 ml) = Predicted increase in blood lead concentration;
BB (mg) = Potential increase in total body burden;

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L ($\mu g/m^3$) = Air lead concentration;
V (m^3/day) = Pulmonary ventilation;
R = Fraction of inhaled lead that is retained;
D (days) = Duration of exposure.

Potential increase in total body burden: $BB = L \cdot V \cdot R \cdot D \cdot 10^{-3}$.

Arbitrarily setting $V = 15$, $R = 0.37$, for the 10.9 $\mu g/m^3$ exposure:

$$IBL_H = m_H + b_H \log_{10} BB;$$
$$IBL_H = 6.80318 + 10.8101 \log_{10} BB;$$
$$(r = 0.97).$$

Similarly for the 3.2 $\mu g/m^3$ exposure:

$$IBL_L = m_L + b_L \log_{10} BB;$$
$$IBL_L = 4.283 + 3.774 \log_{10} BB;$$
$$(r = 0.92).$$

In order to calculate increases in blood lead concentrations resulting from air lead levels lying between those used in this study, the following relationships are used:

$$\Delta m = m_H - m_L;$$
$$\Delta b = b_H - b_L;$$
$$L_H = 10.9\ \mu g/m^3;$$
$$L_L = 3.2\ \mu g/m^3;$$
$$\Delta_L = L_H - L_L;$$
$$IBL = \frac{L - L_L}{\Delta_L} \Delta m + m_L + \left[\frac{L - L_L}{\Delta_L} \Delta b + b_L\right] \log_{10} BB.$$

Simplifying and substituting:

$$IBL = 0.327L + 3.236 + (0.914L + 0.85) \log_{10} BB.$$

Figure 1 shows a semi-log plot of increase in total blood lead content and potential increase in body burden. Again, pulmonary ventilation is arbitrarily set at 15 m^3/day, retention at 37% and blood volume at 4.9 liters. For the exposure to a mean level of 10.9 $\mu g/m^3$ of lead aerosol: $y = 0.33 + 0.53 \log_{10} x$. For exposure to a mean level of 3.2 $\mu g/m^3$ of lead aerosol: $y = 0.21 + 0.18 \log_{10} x$. Figure 2 shows the same plots without transformation as well as two curves predicting the results of intermediate exposures. Those plots indicate that toward the end of the actual exposures, approximately 10% of the potential increase in body burden could be accounted for by increased total blood lead content. This figure agrees in general with the observations of Schroeder and Tipton that as equilibrium is approached, about 90% of the total body burden of lead is in the skeleton [3]. If one assumes that circulating blood volume represents a compartment with a turnover rate considerably greater than that for bone, it is seen that this fast compartment reflects small increases in body burden at the beginning of exposure, but as exposure is prolonged a continuously

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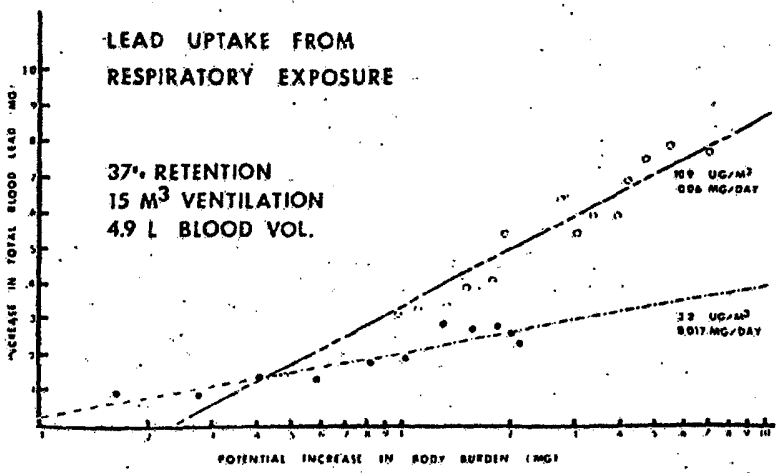

Fig. 1

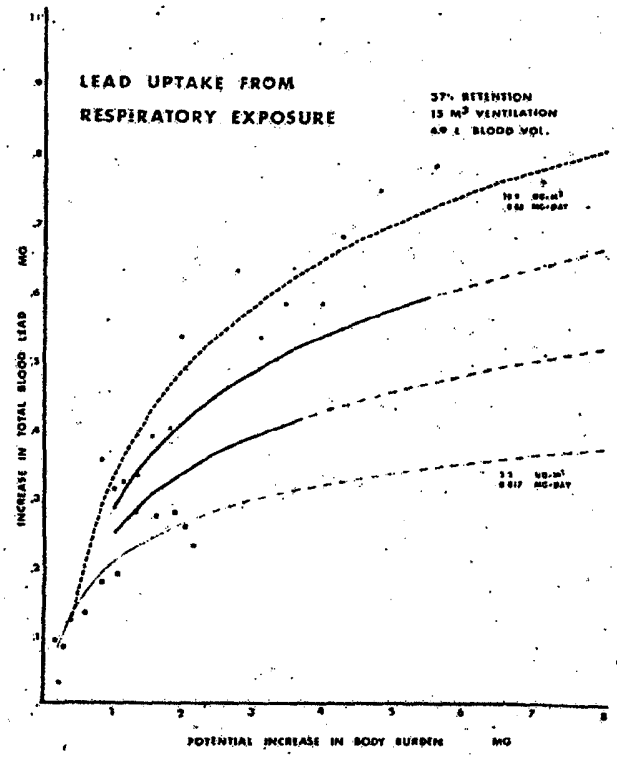

Fig. 2

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TABLE 1

Predicted increase in blood lead (μg/100 ml) *for representative exposures**

Air lead (μg/m³)	Days of exposure			
	25	50	75	100
4	3.4	4.7	5.5	6.1
6	4.7	6.6	7.7	8.5
8	6.2	8.7	10.1	11.1
10	7.9	10.9	12.7	13.9

* Pulmonary ventilation = 15 m³/day
Retention = 37%

increasing fraction of increased body burden can be accomodated in the slow compartment. Thus continued exposure to even low levels of atmospheric lead may result in significant increases in total body burden without proportionate increases in blood lead levels. This concept supports the observations of those investigators who have found age-related increases in bone lead concentrations [3, 4] and the conclusions of tracer studies in animals [5–8]. Similar age-related increases in blood lead have not been found [9, 10].

5 — DISCUSSION

Interpretation of data in a way that allows one to predict the outcome of future experiments is a pastime that is often amusing, at times helpful, but always hazardous. Assumptions inherent in development of the argument may go unrecognized or be misinterpreted. The temptation to extrapolate beyond the data always exists. Yet, when experiments as time consuming and costly as these are performed, one feels compelled to extract as much information as possible from the results. When the subsequent experiments cannot be done, a model makes possible best judgment decisions based on available information. When they can be done, the model should assist in improving their design efficiency. We hope, therefore, that any predictions based on the calculations developed here, will be interpreted with great caution. Extrapolation beyond the exposure levels or duration of exposure used in this study may not be valid.

Retention rates for lead particulate of respirable size has been estimated by several authors [11–13]. These rates may range from about 30% to 50%, but 37% is

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frequently used as an arbitrary intermediate figure. Pulmonary ventilation depends on level of metabolic activity and can range from 10.8 m^3/day for a sedentary man to 22.8 m^3/day for one engaged in light activity [14]. The men in this study were not entirely sedentary, but space restrictions prevented normal activity. We chose to use an intermediate value of 15 m^3/day. Blood volume was not measured in the subjects participating in this study. The value of 4.9 liters was used for the calculations presented here.

In this report we have emphasized increases in blood lead content because we wished to study its relationship to potential increase in total body burden. We could not measure baseline total body burden in these subjects, so only potential changes could be used in the modeling. We did measure baseline blood lead concentration before exposure began (19.6 ± 4.8 μg/100 ml). This is a level somewhere between that reported for rural and city dwellers [10]. For this reason we believe predictions based on this model will be relevant to a large fraction of the general population.

It is very difficult to compare the results of these analyses with those done by others. The kinds of assumptions and manner of presenting data are so varied that we have elected not to attempt comparison. Validation of the model will depend on future experiments. In the meantime, however, internal consistency of the model has been demonstrated by different methods of analyzing the same data which results in substantially the same predictions. Details and results of these analyses will be the subject of future reports.

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DISCUSSION

WILLIAMS (U.K.)
The speaker refers to one paper which says that symptoms and signs occur at blood leads of 40-50 µg/100 G. This is a rather freak paper. I would draw his attention to a paper in the B.M.J. signed by about 18 experts who said that symptoms and signs do not occur at blood leads of less than 80 µg. 100 G. Also, could his results differ from those found with antiknock lead because of differences in the aerosol?

KNELSON (U.S.A.)
I appreciate your concern with arbitrarily defining a narrow range of blood lead concentration at which symptoms may begin to occur in some individuals and recognize this point is still a subject of controversy. On the other hand, in the NAS monograph attention was drawn to the fact that clinical signs and symptoms are not always reliably related to blood lead concentrations. Many occupationally exposed workers appear to be symptom-free at levels above 80 µg/100 G whereas overt toxicity occurs in other individuals at substantially lower levels.
With respect to composition of the aerosol generated in this study compared to that occurring as a result of automotive emissions, I would like to make these observations: Dr. Lawther just showed us many pictures demonstrating the great variability of lead-containing particles occurring "naturally". Electron micrographs made of the artificially generated particles show many of the same characteristics of aggregation. There is not, of course, any organic matrix in the chamber aerosol. Neither is there an appreciable amount of lead halide compounds. At the concentrations of lead aerosol in this study, and those occurring naturally, however, it seems likely that any particles will either go very quickly into solution or be ingested and digested by pulmonary alveolar macrophages.

CRAMER (Sweden)
I would like to say to Dr. Williams that I am sorry that I can no longer support the view that no lead poisoning occurs below 80 µg 100 ml. It occurs, according to my opinion, although it may be rare. The data of Dr. Knelson once more make me doubtful about the conclusions from the Seven City Study, presented by Dr. Cole yesterday on behalf of ILZRO. If you omit the point at the extreme right of his figure 5, there must exist a positive correlation between lead in air and lead in blood. How valid are the data from Pasadena, i.e. your point with the highest lead exposure?

COLE (U.S.A.)
Referring to Dr. Cramer's suggestion that elimination of the upper right hand value in the air-lead vs. blood-lead curve of the Seven City Study would give a significant regression, I feel that it is not justified to eliminate a set of approximately 200 of 2000 data points without scientific justification.
The particle size and form of the lead particles and the lack of extraneous particulate material in the inhalation chamber was quite different from that quoted by Lawther in his samples of atmospheric lead particles. Would this not affect the absorption of lead from the lung.

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KENNEDY (U.S.A.)
What was the general health of the volunteers prior to and following exposure to lead in the chambers? (Excluding the effects such as increased lead levels, ALAD activity?)

KNELSON (U.S.A.)
Their health was normal as determined by routine medical history, physical examination and clinical chemistries. None of these parameters deviated from normal limits throughout either exposure period for any subject.

KENNEDY (U.S.A.)
Could you comment on the period of exposure required to reach blood lead equilibrium? It would appear from the data (10.9 $\mu g/m^3$) that this point was reached between 120-170 days of exposure.

KNELSON (U.S.A.)
I don't know when equilibrium occurs. Casual inspection of the data suggest equilibrium was attained within the period of study. Models that are not yet in equilibrium, however, account for as much as 92% of the variance in the experiment. I think the subjects of this study were nearing equilibrium, were approaching asymptotically a limit, and the distance from such a limit was probably of about the same magnitude as the "noise" in the measurements.

KENNEDY (U.S.A.)
Could you comment on the time required for blood lead levels to return to pre-test levels following cessation of exposure to the lead in the chambers?

KNELSON (U.S.A.)
We are still analysing the data concerning return to baseline levels.

GUINEE (U.S.A.)
According to your calculations a lead air concentration of 10 $\mu g/m^3$ breathed at a rate of 15 m^3 per day would yield an exposure of 150 µg per day, one third of which is retained or 50 µg. Why do you think 50 µg which enters by the airborne route is reflected in the blood whereas an increment of 50 µg via the diet would probably not cause an increase in the blood lead level?

KNELSON (U.S.A.)
Well, I don't pretend to understand all the details of gastrointestinal vs. respiratory lead uptake. So I can only speculate on those relationships. However, the generally accepted figure of 10% retention of GI-dose must have a considerable damping effect on any fluctuations in dietary lead.

WILLIAMS (U.K.)
How does Dr. KNELSON account for the apparent conflict between his results and those of the Seven City Survey: And I might comment that it is more important what happens in cities than in penitentiaries.

KNELSON (U.S.A.)
Interpretation of data from the "Seven City Study" is still under discussion. As for your remark that what happens in cities is more important than in penitentiaries, I assume it is facetious. One is probably an important function of the other. With respect to our discussion of lead uptake, however, I believe the problems of simulating ambient exposure conditions for the purpose of carefully controlled clinical studies are no greater than the problems inherent in the large number of uncontrolled, and uncontrollable confounding covariates in population studies.

SANSONI (Federal Republic of Germany)
According to the writer, *artificially* manufactured lead-containing aerosols chiefly contain α PbO_2. Is this compound also the main source of lead in *natural* lead-containing dust? If not, to what extent can the results obtained be extrapolated?

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KNELSON (U.S.A.)
In addition to the lead oxides, natural lead containing dust includes some halides as well as a variety of other materials that may be contained in street air and included in the particulate aggregate. Dr. Lawther discussed these factors with much more authority than can I. Because of the comparatively very low concentrations of Pb in the inhaled air, even the relatively insoluble lead oxides must be expected to go quickly into solution. The more amorphous particles are probably ingested and digested by macrophages with resultant ionic Pb rather than any particular Pb compound.

CLAYTON (U.S.A.)
Please briefly summarize the health status of your subjects especially in relation to time. Even though your paper's title does not necessarily require this, it would seem to be needed because of the objectives of the symposium.

KNELSON (U.S.A.)
Among the many criteria for inclusion in the study were those concerning the health status of the subjects. In brief -- they were required to have no chronic or acute diseases detectable by ordinary medical history and physical examination. In addition, they all had normal baseline ECG, chest film, urinanalysis, hemogram, SMA-12 screen, urinary ALA, erythrocyte ALAD, and blood lead. Although some of these values changed during the study, none were outside normal limits. Any changes in "health status indices" were, therefore, subclinical, although in some cases statistically significant changes occurred.

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