CONFERENCE ON INORGANIC LEAD

AMSTERDAM, NOVEMBER 1968

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SESSION I - BIOCHEMISTRY

Chairman: Professor Tiesinger

De Bruin presented his paper and also mentioned some new findings.

Discussion: it was suggested that the presence of reticulocytes was as good a measure of lead exposure as "stippled ~~cells~~ since the increase in ~~stippled cells~~ and lead exposure ~~was~~ parallel ~~but~~ although the reticulocytes increased first. This was countered by the suggestion that the reticulocytes were less specific ~~for~~ lead ~~exposure~~ than punctate basophil ~~cells~~. Several speakers said that because of the high variability both in response and in the method of measurement, reticulocyte counts were not an adequate ~~guide to lead exposure~~.

Turning to the correlation between various enzyme changes, it was pointed out that the absence of a good correlation between the various tests, although expected, should not lead to the rejection of new findings. It was generally accepted that in vitro experiments with erythrocytes cannot be directly compared with in vivo findings.

Gajdos said that ~~for~~ 24-hour urine, ~~samples~~, an increase in -aminolaevulinic acid greater than 20 mg/l, ~~of~~ coproporphyrin, 400 ug/l, ~~of~~ uroporphyrin, ~~a~~ slight increase or ~~absence~~, ~~and~~ increased protoporphyrin in erythrocytes, were specific ~~for~~ lead absorption. There was no general dissent from this statement, ~~decision~~ on whether all these tests were

necessary in ~~plant control,~~ the control of lead hazards in industry; the matter was left for later discussion. Because the use of chelating agents either prophylactically or as a provocative diagnostic test alters the levels of coproporphyrins and other biological measurements, no reliance should be placed on them under conditions associated with the use of chelating agents.

Persistence of ~~raised~~ elevated amounts of protoporphyrin in the erythrocytes up to eight years after ~~exposure was~~ the discontinuance of significant exposure to lead, might well be important from a medico-legal point of view.

Discussion then returned to what measures ~~indicated~~ were indicative of risk in the case of the exposed workmen. The primary indication of risk, of course, is the ~~lead risk.~~ It was suggested that the most important ~~factor was~~ indication of actual ~~is~~ → the attack on the ~~red cell~~ erythrocytes. This suggestion received support but was qualified by stating that the measurement would vary with the method used to determine the survival time of ~~red cells~~ erythrocytes. Because of the removal by the spleen of abnormal ~~red cells~~ erythrocytes, the life cycle of these cells in the peripheral circulation was very short compared with normal cells. It was concluded that, in the absence of gross anaemia, the bone marrow was producing very large numbers of stippled cells and reticulocytes during increased lead intake.

(In the blood until it reaches the critical level of 0.08 mg. progressive increase in the lead concentration of tissues)

Morphological changes, including mitochondrial swelling and vacuole formation in erythrocytes, when seen under the electron microscope, were ~~noted.~~ mentioned in this connection. ~~These changes~~

It was also mentioned that lead was found in high concentration in the liver mitochondria ~~after short exposure of~~ of the rabbits after brief exposure to the fumes ~~to~~ heavy doses of lead. Experimentally, it required large quantities of lead In answer to a question on the relationship between the microsome and the mitochondria, it was said that lead was known to affect mitochondria in the bone marrow, liver, and the

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renal tubules. In the bone marrow, the effect of lead on mitochondria was a primary one, ~~and~~ in which the mitochondria were frequently damaged. They do not take part in the formation of stippled ~~cells~~ erythrocytes, but the ribosomes do ~~take part~~ participate in their formation.

Lead is found in high concentrations in the ~~liver~~ hepatic mitochondria of rabbits after a short ~~exposure~~ period of severe exposure to lead. The changes in the renal tubular mitochondria due to lead ~~were~~ are similar to those seen in the bone marrow.

A question on the effect of lead on mature red cells was not resolved.

The practical significance of ALA dehydrase was regarded as limited, because it ~~was~~ is easily inhibited by lead and there was very little difference between ~~a~~ mild and severe exposure to lead in this respect, the effect upon this ~~and dehydrase~~ activity would not, therefore, have diagnostic value.

It was queried whether a so-called normal level of concentration of lead in the blood, had been established ~~was already~~ ~~altered by normal ambient lead levels.~~ as regards the lead found currently in the ambient atmosphere It was stated that 5-hydroxyindolacetic acid was ~~raised 60%~~ increased by 60 per cent in the whole blood of exposed subjects, as compared with controls. When exposed to 0.3 - 0.4 mg/M^3 Pb, the values rose from 10 ug/l to 16 ug/l in whole blood.

Hernberg, commenting on his paper, was not able to explain the relationship between ATPase and potassium ion efflux from red cells, but he ~~mentioned~~ stated that different storage conditions in tracer experiments gave different results on the rate of potassium influx and efflux. If potassium loss is high in vivo, the cell will die and be removed from the circulation.

The importance of SH groups in relation to the effects

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of lead on enzyme systems was mentioned, but it was said that not only SH dependant enzymes were affected by lead. It was noted that the presence of EDTA, in vitro experiments, would prevent the effect of lead on SH groups.

The relevance of such concentration to the levels in human blood in industrial exposure, was then queried. In reply, it was stated that 10^{-1} moles per gram of lead had been used, and that this was about 150 times the concentration of 80 micrograms per 100 grams of whole blood.

It was noted that Westerman had found similar concentrations in the bone marrow when the blood contained 100 micrograms percent of lead.

Albahary, presenting his paper, said that there was little departure from the normal types of haemoglobin in saturnism and that this fact was important in Mediterranean countries because of the differential diagnosis from thalassaemia, when the foetal type of haemoglobin occurred in high concentration. Lead causes some variation in the foetal type of haemoglobin, but only in children up to six years of age.

In adults, an increase in the foetal type of haemoglobin only occurs in severe cases of lead poisoning.

In lead poisoning, HbA_2 varies linearly with haemoglobin, and although the mechanism is not well understood in plumbism, there is a reduction in β chain and an increase in α chain.

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SESSION II - CONCEPTS OF LEAD INTOXICATION

Chairman: Professor R.Lane

Lehnert introduced his paper and suggested that:

1. Lead poisoning is not necessarily directly related to the degree of absorption or dose, although the dose must be adequate
2. There are wide ~~discrepancies~~ variations in the results of many of the laboratory tests and also, unfortunately, wide discrepancies in the results reported by different laboratories.
3. On first exposure, men may exhibit mild symptoms which then resolve.
4. There is an increased in sensitivity to lead after an episode of poisoning.

Asked for experimental evidence to support the cybernetic approach, the speaker replied that it was largely hypothetical but that these facts may be understood by such an approach. It is difficult to fix TLVs, except at the minimum threshold of response, because the organism is capable of accepting certain doses without clinical manifestations. Feed-back mechanisms, when the body reserves are depleted, will lead to functional loss increasing with absorption.

Kehoe objected to the concept of the apparent absence of any dose/response relationship. Lehnert replied that this was due to the variability of the sensitivity among individuals and in the same individuals under different circumstances, ~~variations~~, but went on to say that what he meant to stress was that ~~high absorption~~ the absorption of large quantities did not equal poisoning.

Attention was drawn to the differences between acute and chronic poisoning. Many animal experiments were of an acute nature, and there was a tendency to draw general conclusions from these. The speaker agreed that it was easier to predict the effects of an ~~acute~~ brief high dosage than ~~long-term~~ of prolonged low dosage, because at low

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dosage rates there is no sharp increase in the ~~blood~~ concentration in the blood ~~due to a balance mechanism~~.

Comment was made on the different effects of ~~high, acute~~ brief, severe exposure, such as shipbreaking, and the slow, ~~chronic~~ prolonged effects in battery workers.

Some ~~people had~~ of the group found Lehnert's paper difficult to understand, but it was thought that ~~the~~ his mechanistic approach was useful and general ~~one~~ to all types of poisoning.

Cramer had plans to study δ-aminolaevulinic acid in urine to answer the question whether this index was of greater value ~~for acute~~ in brief, severe exposure and whether urinary ALA values increased more rapidly in such circumstances than did blood lead levels.

Williams and Zielhuis then presented their joint paper. In comment, Williams said that we cannot measure lead absorption precisely, and we should use this word more carefully. What is an unacceptable response? What matters in regard to fixing this level is the effect on the motor system or "sense data," not biochemical effects. The word 'poisoning' according to these authors, should be reserved for its major clinical ~~effects~~ manifestations, rather than those which may be no more than biological phenomena.

In response to Williams' statement that lead absorption could not be measured directly, Cramer stated that he found this paper confusing and of little help. He considered that absorption can be measured indirectly with blood lead. The real issue was the definition of poisoning, and he would agree with the authors if they would add the provision of "unlimited spare-time activity" to their

~~[illegible]~~ * Abnormalities indicated by sensory perception, ie subjective.

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definition as well as "prevent[ion] of gainful employment". That is, the workman should not suffer impairment of function, or economic loss, although there are, admittedly, socio-economic problems associated with so broad a definition. ~~He also accepted that there were socio-economic problems.~~ The conference accepted the definition.

It was stressed that we must consider the whole man, from the least ~~first~~ biochemical changes to the more obvious injurious effects ~~and then further effects~~. Epidemiology may be an aid in this problem. Williams himself had shown that personal samplers gave a good indication of the effective (individual) exposure ~~absorption~~.

Another speaker mentioned that "poisoning", particularly for medico-legal work, must be a matter of clinical judgment. However, prevention was more important. The real problem for the conference was "what constitutes permissible exposure?"

The next speaker supported this idea but stated that he could not accept socio-economic factors in the determination of accepted levels. The conference should separate medical and social acceptability, and keep to the former. Anything that impaired health was regarded as medically unacceptable. Some workers who do not complain of poisoning feel better following their removal from work involving exposure to lead ~~lead work~~. The speaker regarded this type of change as indicative of ~~unacceptable~~ exposure, ~~and~~ suggested that this was, in fact, early poisoning when it could be fairly judged to be valid clinically.

Complex social factors make it difficult to decide whether to allow men to continue at work at or above accepted maximum safe levels of blood lead or other criteria. Doctors should attempt to stick to ~~the~~ specific medical criteria, but there were countries where, because of ~~due to~~ malnutrition, the whole population had a low haemoglobin and in some circumstances, probably with a

poor expectation of life, a job along with a low haemoglobin was better than no job, and might increase life expectation.

Zielhuis thought that too much emphasis was being placed on poisoning, and not enough on what was an unacceptable response. Threshold limit values were not believed a universal basis for medical decisions, which might vary with circumstances of and would vary from country to country. "Acceptable" did not always mean desirable.

The acceptability of blood lead levels was then discussed. Zielhuis said that if the blood lead level stayed below 80ug Pb/100mls, peak exposure was unimportant. When pressed to say if this figure was safe, he stated that he thought errors in the estimation would reduce the safe level to 70ug Pb/100mls to give an adequate margin for safety and experimental error.

Professor Kehoe agreed with Professors Lane and Zielhuis in accepting 70ug Pb/100mls blood as the upper limit of safety w.r.t. TLV. Not allowance for analytical variation (deviation).

Referring to definitions of absorption and poisoning, Williams said these should be dictionary definitions and not decided separately by individual doctors. He raised the question as to whether a decrease in ALA dehydrase should be compensatory or intoxication. Kehoe thought not, in the present state of our knowledge. The question is this relationship should be whether this is regarded as sufficient cause for the discontinuance of gainful employment.

Williams accepted the W.H.O. definition of health, but said that acceptability depended both on time and country (ie knowledge and social sensitivity, Editorial interpretation).

Malcolm suggested the use of an international questionnaire addressed to various experts in an attempt to relate biochemical to other findings. He thought that there should be an agreed medical standard but recognised that nations

might not be able to adopt these at a particular period of time. The definition of ~~absorption~~ The significance of exposure would be clarified by the experimental use of personal samplers to relate environmental to biochemical and clinical findings. There was also a need to define toxicological parameters parallel to the clinical statement published in the British Medical Journal.

~~The word "absorption" should only be used where no~~ The term "lead absorption" should not be used to cover any result of environmental exposure to lead in which any departure from normal well-being ~~can be measurable or~~ occurs is likely to occur. Including the term ~~has no quantitative~~ significance, nor any relevance to hazard. Its uses should not be allowed to hide any deleterious effects of the absorption of lead. Lead poisoning is a clinical term, but the current concept is likely to change ~~in the future~~ in some respects as it has over the last ten years. Through new information

Acceptability should depend on the absence of any effects on the well-being of the individual.

On Professor Zielhuis' recommendation, the conference accepted this definition.

It was agreed that the presence of symptoms of illness equated with poisoning. Zielhuis stated that the conference should not determine the meaning of illness philosophically, but by way of information and data, ~~philosophies but provide data~~.

SESSION III - DOSE/RESPONSE RELATIONSHIP

Chairman: Professor R.Kehoe

Williams introduced his paper. The first speaker in the discussion thought that this was one of the few papers that covered all the variables but questioned the use of the Donath scale for urinary coproporphyrin. Williams said that although this was a semi-quantitative method, the mathematical correlation gave an acceptable method of indicating lead absorption. It was suggested that the relationship should be curved and not linear, but Williams said that the regressions were tested within limits for linearity.

Another speaker thought the statistics did not prove linearity. It was observed that Williams' use of the personal sampler gives better regressions than static samplers, and it was suggested that personal samplers should be used to fix MACs and TLVs

Cramer suggested that on Williams' evidence, 15 mg urinary δ-aminolaevulinic acid should be used as the ~~HSC~~ maximum acceptable level and asked whether there was a possibility of diurnal variation or day to day variation in the levels of ~~UALA~~. δ-aminolaevulinic acid in the urine

Williams replied that all his samples were taken at the same time of the day and that a further paper on diurnal variability was in preparation.

It was suggested that the paper should have contained confidence limits. The speaker said this had been done in another paper and all the relationships except haemoglobin were significant.

It was accepted that the data were useful in setting MACs.

Professor Kehoe then showed slides illustrating the response of human subjects to uniformity of the airborne lead ~~against blood lead in volunteers who were standing and doing moderate work.~~ as shown by the concentration of lead in their blood and by the excretion of lead in their

It was stated that ~~the activity was normal at an air~~ Normal respiratory activity involved The consumption of about 5 M^3 per eight-hour day. It was suggested that 10 M^3 per eight-hour day would be more appropriate to many types of industrial work.

Another speaker suggested that it was important to define the particle size and distribution ~~in relation to MACs. It was~~ as a part of the specification, in relation to the setting of a standard of tolerability. It was agreed that the ~~real~~ relationship between particle size and absorption ~~was not completely~~ is not known, quantitatively.

SESSION IV - THE CHRONIC EFFECTS OF LEAD ABSORPTION

Chairman: Professor Beritic

Urbanowicj introduced the paper by Kosmider and emphasized the following points:

1. No conclusion can be drawn about the effects of lead absorption, or the subsequent biochemical changes, on the vascular system.
2. The influence of lead on the blood vessels was mediated through the autonomic nervous system rather than by a direct effect of lead on the vascular wall.
3. ~~Animal work was not always~~ Observations on animals were directly related to human experience.
4. Variations in the electro-cardiogram due to the effects of lead were shown on slides.

The first speaker was surprised that systolic murmurs had been heard. He had neither found nor suspected these in cases of lead poisoning.

It was suggested that the ECG changes would only be convincing if the controls were properly chosen. This was not clear from the paper.

It was then suggested that the effects of poisoning were not relevant to the discussion on TLVs.

Urbanowicj promised to refer these queries back to the author.

As Professor Albahary had had to leave the conference, his paper was open for discussion.

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In general the conference felt that reports of clinical cases were not relevant to ~~setting TLVs~~ the determination of standards for the purpose of preventing illness, and discussion was curtailed.

Malcolm then introduced his paper. He stated that it was important that ~~TLVs and MACs~~ standards of safety should not only prevent departures from normal well-being in the short term but should also prevent any long-term sequelae.

Lane reported that his original work on causes of death in three battery factories had shown an increase in cerebrovascular deaths and that these were related to lead levels of about 0.5 ~~mg~~/M^3 (0.5 mg./M^3) for many years of exposure, and he emphasized the difference between organic and inorganic lead.

The next speaker agreed with Lane that kidney damage arose from heavy dosage. He showed slides suggesting an increase in incidence of hypertension and albuminuria 15 years after episodes of colic.

It was suggested, regarding Malcolm's data on the lack of any effect of degree or time of lead exposure on blood pressure, that ~~exposure time was~~ the duration of exposure to lead is related to age, which of itself could obscure the effect of lead. Group comparison, age for age, was necessary.

Malcolm stated that over 1,000 measurements of blood pressure had been made and that these gave no ranking order association with lead exposure, and that the average age of the group was 45 years. One speaker suggested that because of the effect of age on blood pressure, the findings ~~could~~ might imply that lead lowers the blood pressure. There was some pharmacological support for this idea.

It was generally agreed that long-term sequelae were

prevented in groups which were adequately controlled to avoid any departure from normal health, but that long-term sequelae occurring subsequent to episodes of poisoning were not relevant ~~to establishing~~ to the consideration ~~bias~~ of hygienic standards.

Professor Beritic referred to the endemic nephritis in Yugoslavia. He had seen many cases of lead colic but only transient kidney lesions. He said that cancer was reported to be rare at Trepča where all of the inhabitants were ~~all~~ exposed to lead. ~~A high dose~~ Large dosages administered to of lead ~~is~~ rats gave rise to renal cancer. Williams referred to the work of Lillis et al, published in the British Journal of Industrial Medicine, showing long-term renal lesions following repeated episodes of colic and observed over a long period. Beritic reported that ~~also~~, 30 workers removed from lead at the Trepča lead works 15 years ago had no renal lesions, but EDTA had been used in their treatment.

Cramer stated that he had found a low incidence of hypertension with no long-term effects in battery workers in 20 years' follow up despite bad conditions, and another speaker supported these findings.

Malcolm accepted that no renal lesions occurred after a single attack of poisoning, but considered that some cases of chronic interstitial nephritis would occur ~~after~~ in association with repeated attacks of poisoning and continued heavy exposure to lead over many years.

It was suggested that the long-term effects following repeated episodes of poisoning were not ~~relevant to the~~ of concern to this conference.

Another speaker stressed the long time which was required for lead levels to reach normal after being increased.

Professor Beritic then summed up.

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SESSION V - INTER-RELATIONSHIP OF PARAMETERS

Chairman: Professor Vigliani

Zielhuis introduced his paper.

Williams then presented his paper and emphasized the low correlation of haemoglobin with all other indicators and reported that analysis of a further 250 samples still indicated no correlation between haemoglobin and blood lead.

King then presented his paper and indicated that he would accept curve relationships between some of the parameters but had plotted linear because of the scatter and the width of confidence limits.

Malcolm produced data for workers at two battery factories, also revealing no correlation between haemoglobin and blood lead. This data included all individuals with blood lead concentrations in excess of 80ug% at the first factory.

He stressed that both his and Williams' data were derived from factories where increases above the acceptable limits had led regularly to prompt action.

Stopps then presented data supporting Malcolm and Williams, showing no correlation between blood lead and haemoglobin. Data plotted from the literature N = 153 mean PbB of 89.9 and mean haemoglobin of 12.6 ug%. A five-year study at Du Pont of 202 employees and also in a storage battery manufacturers of 109 employees failed to indicate any correlation.

The first speakers agreed that it was most important that blood lead measurements should be taken concurrently with

exposure if misleading results were to be avoided. Rainsford's results were quoted in support of Zielhuis' findings of a correlation between increase in blood lead and a fall in haemoglobin. It was pointed out that in Rainsford's two studies, the first had referred only to factories reporting low haemoglobins. These were poorly run factories and high blood lead levels were found. In a later study of good factories, Rainsford had found normal haemoglobin levels.

Zielhuis maintained that there was no bias between good and bad factories and he considered Rainsford's data to be valid.

It was pointed out that the difficulty of comparing results from different investigations due to the different time intervals between exposure and measurement. In addition, where employees started with a low haemoglobin, it was more likely that there would be a further decrease.

The next speaker referred to the effect of iron deficiency, for example, that reported by Goldberg in the Glasgow area, where 80% of the population were affected compared with London where there was no iron deficiency.

An objection was made to the use of group data for statistical analysis unless reliability of the groups ~~were~~ had been established by rigorous testing of individual points. When this could not be done, it was pointless to plot group data.

King pointed out, however, that his data ~~was~~ were plotted on the basis of individual results for non-selected labour force

not subjected to lead control. The regression lines for groups and individuals were very similar, and this supported Zielhuis' use of group data.

It was suggested that better correlations might be obtained if blood lead values were expressed ~~as a weight percentage~~ in relation to the weight of erythrocytes rather than whole blood.

Stopps reported his study of haematocrit and blood lead levels in 433 workers. Haematocrit levels varied between 21 and 54, blood lead levels varying between 2 and 147ug%, but there was no correlation.

A reduction in haemoglobin was not really a direct response to the "dose" of lead in the blood but a failure of the haemopoietic system. A fall in haemoglobin is a serious response. Since there ~~were~~ are various mechanisms to restore blood, it was probably better to correlate blood lead with reticulocytes. In time, it might be better to measure the activity of other early indications.

The discussion centred on the merit of using haemoglobin itself as compared with the use of a haemoglobin/blood lead correlation, to justify (a) a reduction in working levels and (b) these or other biochemical indicators. It was suggested that a fall in haemoglobin due to lead absorption was not acceptable and therefore should not be used as a primary means of estimating or identifying hazard for the purposes of prevention.

It was suggested that measurement of the haemoglobin level was less satisfactory than the measurement of change in haemoglobin on an individual basis. This might yield different

regressions.

Beritic then introduced his paper dealing with changes in reticulocyte and ~~stippled cell counts~~ the enumeration of stippled erythrocytes and myelocyte/erythrocyte ratios in the bone marrow.

A decrease in haemoglobin ~~level~~ in association with a decrease in reticulocytes ~~levels~~, and an increase in stippled ~~cells~~ erythrocytes should be added to Gajdos' observation about the specificity of increases in ALA, coproporphyrin, and ~~red cell~~ erythrocytic protoporphyrin in lead poisoning. he believed,

The chairman considered, however, that blood lead gave the best correlation with lead exposure.

Zielhuis queried the level of 80ug% for blood lead as a biological TLV with respect to a significant fall in haemoglobin.

It was pointed out that while ~~the~~ a fall in haemoglobin at this level may be statistically significant, it was not necessarily meaningful if small. Moreover it does not always occur.

It was then suggested that haemoglobin surveys should be extended so that changes in individual levels were examined. The speaker accepted ~~80ug% as a biological~~ the value of 80ug of lead per 100 grams of blood permissible limit ~~but~~ in men, but considered it might be a little high for populations not under continuous medical control, especially in view of the analytical deviation.

Kehoe stated that 80ug could not be used as an absolute figure without regard to the accuracy and reproducability of the analysis, even in the best laboratories, and referred to the recent American surveys. He questioned the accuracy of ~~much~~ many of the reported data for blood lead because of varying methods. He had, however, observed cases of lead poisoning in individuals at a reported level of 80ug%, but he insisted that it included a

possible laboratory error of 10%.

Zielhuis, applying Kehoe's 10% error, suggested that to safeguard workers' health the blood lead limit should be 70ug% which could be ~~prevented when~~ accepted as satisfactory for purposes of prevention, in association with lead in urine of not > 130ug/l,

ALA level of not > 10ug/l,

CP level of not > 300ug/l,

taking into account confidence limits.

It was then proposed that an analytical comparison exercise should be carried out to check the consistency and uniformity of data from different laboratories. The speaker referred to the variation of up to 20% in the results of samples he had exchanged with other laboratories. He suggested that the analysis of lead in urine might prompt a greater degree of comparability.

Professor Kehoe said that lead in urine ~~might be suitable for a group but could not be used satisfactorily for the control of individuals.~~ the determination of is a satisfactory means of following the severity of the exposure to lead, if it is carried out in such a way as to compensate for the intrinsic variability of the excretion of lead. This means frequency of sampling or volume sufficient to yield the general level of the rate. The idea of analytical comparisons was supported and reference was made to previous symposia in Paris and Prague.

It was also urged that all laboratories reporting blood lead and other data should be asked to indicate the sensitivity and accuracy of their methods.

Professor Kehoe revealed that in a forthcoming U.S. survey on ambient lead levels in the air, it had been decided to carry out all of the analytical work in one laboratory to avoid

errors and variations found from laboratory to laboratory. He also mentioned that the dithizone method of blood lead analysis ~~was the best established.~~ as currently employed in time-tested laboratories, is the least variable of the methods in use.

Beritic presented his paper on blood lead and lead colic.

The first two speakers revealed experiences of blood lead levels below 80ug% in the presence of colic, but it was not clear ~~whether~~ that the blood lead levels had been measured concurrently with exposure. It was important to ~~determine the~~ would avoid delay between exposure, appearance of symptoms. and the measurement of blood lead levels, and also to know whether the ~~data were~~ resultant level as reported was based on single or multiple determinations.

Beritic said that only single determinations were taken because of the need to treat patients with severe colic.

The need to take more than one sample was emphasized particularly because of ~~errors for small samples.~~ the magnification of error in the analysis of unduly small samples

King had no experience of colic in conjunction with blood lead levels below 80ug in over 50,000 determinations which he had made. Blood lead levels found during colic had ~~no relevance~~ Necessary in the control of lead workers.

Another speaker pointed out that colic was a clinical syndrome not dependent on blood lead level alone.

Cramer and Selander then presented their paper on ALA, blood lead, and lead-in-urine relationships.

The first speaker said that the discovery of an increase in ALA did not necessarily mean that the blood lead levels for purposes of control should be reduced. It was not yet possible

to interpret the clinical significance of ~~a raised~~ an elevation of δ-ALA.

There was then a discussion of the social implications of removing workers with an increased δ-ALA at low blood lead levels from lead work with reference to the law in various countries. This point was not resolved since social systems and allowances were different in each country.

It was suggested that it was possible to have ALA levels in urine even up to 40 mg/l without any certainty of clinical symptoms developing, but Cramer said that consistent levels of 0-40 mg/l were often associated with symptoms.

Stopps then presented his paper on urinary ALA showing a logarithmic curve against blood lead levels in lead workers. This was confirmed by the experience of the first speaker.

Teisinger then gave his paper showing ten years' experience of diagnostic challenge of EDTA. The first speaker queried the advisability of using EDTA for diagnostic purposes.

The chairman suggested that this was a ~~different~~ topic which ~~and~~ should not be discussed at this meeting.

Vigliani presented his paper showing blood lead and lead in urine distributions in urban populations.

The first speaker commented on the high levels and noted little difference between urban and primitive populations in the skewness of the distribution. Commenting on the 2% who had blood leads of between 70 and 80ug%, he thought cases of poisoning should arise.

Kehoe said that such high levels were not found in the

U.S.A. except in abnormal exposure and doubted the analytical methods, which are admittedly difficult.

Schlegel then presented his paper describing monthly screening with urinary ALA and urinary coproporphyrin. Various methods of urinary ALA determination were discussed and it was suggested that the simple methods gave higher levels at lower exposure.

The next speaker said that at his institute the simpler methods had been elaborated in order to be used for screening purposes, and it was commented that the screening method ought to give false high rather than false low results.

The method of Davis et al 35 published in the Archives of Environmental Health was referred to as being quick and good.

Nobody had much experience in the use of the present tube method for urinary ALA measurement, but the importance of PBG interference with ALA was stressed. The speaker said he found the orthodox methods were not difficult to apply at 40 estimations per day and warned of the inaccuracy and non-specificity of the simplified methods.

Stankovic then presented his paper, followed by Urbanowicj's paper.

Comment was made that the ALA and coproporphyrin lines calculated for Urbanowicj's data were lower than those calculated for other work, and Urbanowicj stated that the data came from people exposed for the first time to lead.

Vigliani, in summing up, said ALA was one of the most important parameters for indicating biological response to lead

but much further study was needed to assess the damage or risk to health on a basis of ALA or other biochemical indicators. He also added that the methods for analysis of lead in blood and urine should be checked for comparability.

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