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OR 6-0050

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To All Members of the Health and Safety Committee:

Attached for your information, comments and criticisms is a copy of a work proposal by Dr. Vallee of the Harvard Medical School. As you remember this was discussed briefly at our Health and Safety Committee Meeting as Agenda Item No. 4.

Will you please let me have your thoughts on the suitability of this type of research to meet the industry's needs and whether you would like to make changes and suggestions to Dr. Vallee? When we have obtained your comments we will ask Dr. Vallee to write us a proposal and develop a contract for research which will then be submitted to you for an approval or disapproval.

Very truly yours,

Don G. Fowler

Don G. Fowler, Secretary
Health and Safety Committee

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Look Ahead with Lead

A Biochemical Approach to Lead Toxicity

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The diagnosis of lead poisoning has depended both on the identification of this element in samples of blood and urine and upon the clinical manifestations observed subsequent to exposure. However, the analytical chemistry of lead as well as uncertainties surrounding its metabolism have resulted in major discrepancies of data obtained and of their interpretation. This has complicated the recognition and management of the disease. For the same reasons, the evaluation of the clinical state of industrial workers exposed to this occupational hazard have presented complex problems, both medical and legal.

Efforts to clarify the basis for these uncertainties have not been satisfactory. This may be attributed in large measure to the circumstance that the metabolic role of metals in general, and that of lead in particular, have been understood poorly. It has certainly not been possible to reduce the clinical manifestations to a meaningful set of biochemical denominators.

In recent years much has been learned about the interaction of metals with macromolecules in general and proteins in particular, especially those with enzymatic function. Lead, like mercury, cadmium or zinc, the elements of the IIB group of the periodic system, interacts preferentially with sulfhydryl groups of both simple and complex molecules. Since sulfur groups play a major role both in the stabilization and function of proteins and enzymes, major disorders may be expected when excess quantities of metal are available for interaction with and blocking of these groups. Thus, peripheral neuritis and encephalopathy which accompany

intoxication both with mercury and lead and, of course, other elements has been attributed to the formation of such mercaptides. The therapeutic relief often obtained by means of agents such as BAL is due to their successful competition for the toxic metal ion.

However, not enough is understood currently to integrate the results of sporadic investigations that have been conducted. It seems clear that a more rational diagnosis and therapy could ensue if systematic studies were to be conducted to localize the interaction of lead and to ascertain the stability of the complexes formed and their functional or toxic import.

A number of observations suggest that lead interferes with hemoglobin synthesis and, in fact, at different stages of the synthetic pathway of porphyrins. It has been shown, for example, that lead may inhibit the synthesis of δ-amino levulinic acid from glycine and succinyl coenzyme-A, the synthesis of prophobilinogen from δ-amino levulinic acid; and the synthesis of heme from protoporphyrin and iron. It is known, moreover, that patients with chronic lead intoxication excrete increased quantities of urinary coproporphyrin and uroporphyrin, presumably as a consequence of interference with the same critical steps in the mechanism of heme synthesis.

We ourselves have shown that lead may displace the functionally essential zinc atoms of various zinc containing enzymes, resulting either in complete inactivation or in the alteration of the activities of a given enzyme. It seems most likely that the actual concentra-

tions of lead in serum and urine are but the resultant of the complex interactions of lead with many molecular species that must be expected in a heterogenous environment such as cellular and serum proteins constitute.

We therefore propose to study critically the role of lead in heme synthesis and the resultant changes in serum and urine lead concentrations of living animals, employed as test systems for the models that can be devised. Thus for instance, it would be of great interest to know whether or not lead blocks the metal binding site of transferrin, the iron binding globulin of serum, which is a critical intermediate in iron transport and heme synthesis.

Our laboratory has a longstanding tradition of work in this general area and is fully equipped for analytical chemical work by emission spectroscopy, atomic absorption spectroscopy and microchemical analyses to deal with problems posed either by isolated protein systems or those which may be encountered in living animals and man. We are similarly equipped for all phases of protein chemistry and enzymology.

In the past, our studies have been concerned with the role of zinc, copper, magnesium, arsenic, nickel, cadmium and chromium and our efforts in this regard are a matter of literature record. We feel certain that studies of the type here suggested would clearly advance the aims of the Institute and we would be pleased to make specific suggestions for future studies if this should be desirable.