September 9, 1968

R. S. McCutcheon, Ph.D., Executive Secretary
Toxicology Study Section
National Institutes of Health
Bethesda, Md. 20014

Re: ES-AP-00410-01 TOX

Dear Doctor McCutcheon:

I regret that I have been delayed so long in replying to your letter of August 2. My custom of vacationing in a wilderness in Montana brings my professional activities to a complete halt for a month. I hope, however, that the delay has not rendered my reply useless.

With respect to the likelihood of obtaining highly significant information about the toxicity of lead in low dosage through the study of electroencephalographic tracings in poisoned animals, I cannot muster any very great enthusiasm. The dosages of lead compounds required to induce neurological manifestations in domestic animals are (or appear to be) fairly high. On the other hand, cattle do develop encephalopathic disturbances, and I would suppose that there may well be abnormalities in the brain waves in conjunction with these disturbances.

The most difficult feature of this general problem, experimentally, as it relates to both man and animals, is the necessity of securing quantitative information on the absorption, retention and distribution of lead in the tissues in association with any lesion or toxic manifestation under investigation. How else can one have any appreciation of effective dosage? Almost every initial investigator of the effects of the alimentary intake of lead finds himself utterly astonished by the small proportio of the orally administered lead that is absorbed and distributed to a target tissue. Much experience is required to know just what one is confronted with, by way of dosage and absorption, in an experiment of this type.

Despite what I have said above, these appear to be experienced investigators, embarked upon a systematic investigation of nervous phenomena in relation to a considerable number of toxic compounds which induce neurological responses. It seems logical to them, and it so sounds in their exposition, to include lead in among the substances to be examined. I would hesitate to put obstacles in the way of their program in view of the importance of the lead problem at this time. This is not the way I would approach the problem, but that is neither here nor there.

There is one additional comment which should be made I think. These men are taking much too seriously, in relation to lead in the ambient air, the occurrence of lead poisoning, in its frequent association with encephalopathy, among children. This phenomenon, which characterizes most, if not all, of the older cities of the United States, is not an expression of lead in the air, in any except the unusual situation of gross contamination of the air in a home (or other enclosure) in which lead battery casings (or similar materials) are being burned and the fumes distributed into a confined space. These children, almost as a rule, swallow large quantities of lead (the dosages are enormous as compared with the usual situation in the adult). In consequence, high concentrations of lead are found in the brains of most of those who die with encephalopathic manifestations (values such as 0.30, 0.50, even 0.90 mg.

by the investigators, that little or nothing of importance can be learned about the so-called "subclinical" effects of the absorption of small (threshold) quantities of lead over a prolonged period of time, by setting out to induce clinical lead poisoning in animals through the administration of sufficient dosages. As a preliminary step, however, such a procedure might be employed.

May I therefore, without intentionally side-stepping your question, suggest that this situation is one involving the availability of funds for the pursuit of an intrinsically worthy cause by methods which offer little likelihood of success. The priority, in relation to a large number of other experimental approaches to the same problem, but especially in relation to many other more probably rewarding investigation is not very high, in my judgment.

Sincerely yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wp

Enclosure

UNIVERSITY OF CINCINNATI
COLLEGE OF MEDICINE
DEPARTMENT OF ENVIRONMENTAL HEALTH

KETTERING LABORATORY
JOHN AND BETHESDA AVENUES
CINCINNATI, OHIO 45219

August 5, 1968

R. S. McCutcheon, Ph.D.
Executive Secretary
Toxicology Study Section
Division of Research Grants
Dept. of Health, Education, and Welfare
National Institutes of Health
Westwood Bldg., Room 226
Bethesda, Maryland 20014

Re: ES-AP-00410-01
WRK

Dear Dr. McCutcheon:

Your letter of August 2nd to Dr. Kehoe arrived during his vacation. I shall bring it to his attention when he returns to the office on August 31st and you may expect to hear from him shortly thereafter.

Very truly yours,

Secretary

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AUG 5 1968

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD. 20014
AREA CODE 301 TEL: 656-4000

August 2, 1968

In reply refer to: ES-AP-00410-01
TOX

Dr. Robert A. Kehoe
Kettering Laboratory
Eden & Bethesda Avenues
Cincinnati, Ohio 45219

Dear Dr. Kehoe:

It would be appreciated if you would examine the enclosed application and give us your opinion as to the merits of studying lead toxicity electroencephalographically as proposed by this investigator. The application should be kept confidential and returned to me with your reply.

Sincerely yours,

R. S. McCutcheon

R. S. McCutcheon, Ph.D.
Executive Secretary
Toxicology Study Section
Division of Research Grants

Enclosure

N13166.02

KE 0012517