July 31, 1956

Dr. J. M. Ruegsegger
Lederle Laboratories Division
American Cyanamid Company
Pearl River, New York

Dear Jim:

I hope you will forgive the tardiness of my reply to your letter of June 12th. I've been swamped, and only now, in preparation for a vacation, have I had a chance - or rather manufactured the chance - to take care of letters that were not urgent.

Fairly recently the therapy of metallic poisoning, lead in particular, has been shifted vigorously in the direction of the chelating agent ethylene diaminetetraacetic acid (EDTA) administered in the form of its disodium calcium salt principally. It might be difficult to draw much attention to thioctic acid at present, in view of the largely justified enthusiasm for this agent. However, there are people who are interested in developing new means for the therapy of the heavy metals, and certainly anything that offers hope for a prompt benefit in the treatment of the more severe forms of these diseases will receive attention.

The paragraph in Professor Donatelli's discussion sounds a bit glib and overenthusiastic, particularly in relation to the therapy of mercury and arsenic poisoning, and I should like to see some of the evidence on which his statements are based.

Moreover, I'd like to have some idea of the rationale in the use of the compound in heavy metal poisoning. If you would be good enough to tell me more about this, I'd be glad to put you in touch with some people who could take a look at it. We have a very serious problem of fatal and permanently disabling lead intoxication in children, and I would have no trouble here in trying out a material that could offer real promise.

The so-called prophylaxis of lead poisoning in industry, in my opinion, is not only unnecessary for the solution of the problem, but - worse - it tends to hinder the progress of sound industrial hygiene. The same, in a general way, is true of the other heavy metals as industrial hazards. The way to prevent such poisoning is not therapeutic but preventive in the sense of the limitation of exposure. The latter can

be done, and is being done, where there is a will to do it. Palliative treatment only delays the day when it will be done generally and effectively. I am not objecting here to the medical treatment of people who are ill. I am objecting, strenuously, however, to the medical pandering to the ignorance or social carelessness of industrial management.

Let me know something about the possible or probable usefulness of thioctic acid, and I'll see what I can do about it.

It is good to hear from you again. I shall look forward to doing so again. It would be nice to see you also.

With kindest regards.

Sincerely yours,

RAK:vr

Robert A. Kehoe, M.D.

LEDERLE LABORATORIES DIVISION

American Cyanamid Company

PEARL RIVER, NEW YORK · CABLE ADDRESS: LEDLAB · TELEPHONE: PEARL RIVER 5-5000

June 12, 1956

Dr. Robert A. Kehoe,
Kettering Laboratories
University of Cincinnati
College of Medicine,
Cincinnati Ohio

Dear Bob:

Two months ago I intended to call you in your office when I was in Cincinnati but my plans in Cincinnati were rudely changed.

For sometime we have been conducting some investigations with a synthetic compound variously called thioctic acid, lipoic acid or protogen. While it was postulated by the chemists that it might belong to the Vitamin B group of compounds, its real role in human nutrition has never been ascertained. There has been an inkling in some clinical studies originating in Germany as well as in the United States, that it might be effective in treating patients with hepatic coma. As you will see from the enclosed translations, the Italians have held a symposium in Naples regarding the clinical usefulness of this compound.

I am writing to you particularly in regard to the possible use of thioctic acid in the treatment of heavy metal poisoning. If you know of clinics or industrial hospitals which might be in a position to use this material I shall be very happy to have you refer such places to me. Inasmuch as the compound is fully absorbed when given by mouth it is conceivable too that this might serve as an effective prophylaxis for people who have a high exposure to intoxication by lead and other heavy metals. At any rate, I shall appreciate your ideas in this regard.

With best wishes to you and my many friends around Cincinnati,

Sincerely yours

RESEARCH DIVISION,
American Cyanamid Company

J.M.Ruegsegger, M.D.
Clinical Research Section

JMR:c
Enc

N 6269.01

SUMMARIES OF SIX PAPERS

(Thioctic Acid Symposium, Naples Italy, November 28-30, 1955)

1. Professor Calvin - The Participation of Thioctic Acid in Photosynthesis.

As a C-S-S-C-system thioctic acid is actively involved in photosynthesis and also participates in the porphyrin synthesis. The addition of thioctic acid causes the increase of O_2 by more than 50%. Thioctic acid, however, is probably not an active reactive form of the plant and animal organisms.

2. Dr. Braude -

Dr. Braude developed his own synthesis of thioctic acid in England which differs from the Reed synthesis by the position of the sulfur atoms. Also this synthesis still requires 5 steps of development. He obtained a yield of approximately 30%. Production of thioctic acid is planned to start in England according to the synthesis by Braude.

3. Professor Donatelli, Naples - Pharmacological Studies on Thioctic Acid.

Thioctic acid occurs in all organs with the exception of the thyroid gland. Many organ systems can be activated by thioctic acid. A chemical demonstration was elaborated which, however, still lacks sufficient precision. Pharmacological studies were carried out in cooperation with Professor Pontecorvo. Thioctic acid has a certain bacteriostatic effect on a number of bacteria. In plants, small doses of thioctic acid stimulate growth of roots; high doses, however, have a depressive effect. Therefore, it is believed that large doses of thioctic acid have an effect on tumors. Trials have been made on the following animals: ameba, guinea pigs, mice, rats, pigeons, rabbits.

Mercuric chloride poisoning as well as arsenic poisoning can be influenced better by thioctic acid than by BAL. It has also a beneficial influence on cyanide poisoning. Alloxan-diabetes can be prevented by thioctic acid in experimental dogs. Lead poisoning responds to this therapy. Moreover, all substances promoting acetylisation processes in the body can be inhibited by thioctic acid. Carbon tetrachloride poisoning (CCl_4) can be prevented with thioctic acid. Thioctic acid has no influence on arterial blood pressure. Respiration can be stimulated up to a dosage one hundred times the quantities given to humans. It is still doubtful whether thioctic acid has an effect on the neurovegetative system. There is an increased motility of the intestines by thioctic acid. In animal experiments increased diuresis and biliary excretion are observed. In acute hepatitis the icterus disappears more promptly with the aid of thioctic acid than without it. The kidneys and the liver have the highest thioctic acid content as compared to other organs. It is excreted by the kidneys.

4. Professor Laritza, Sardinia - Pathological Physiology of Thioctic Acid.

Animals are able to synthesize thioctic acid. The range of application is much wider than supposed until now. Trials at the Pathological Institute in Messina with thioctic acid revealed that this substance is in a position to prevent fatty liver. The blood cholesterine values as such are not being changed. The relation of cholesterine to cholesterinester, however, is being

influenced. A combination of thioctic acid with cocarboxylase is less effective than thioctic acid alone. There is a certain interrelation to body-own hormones like the antidiuretic hormone (ADH), cortisone and ACTH. The daily optimal dosage is stated to be 10 - 20 mg.; injection of quantities up to 60 mg., however, is also possible.

5. Professor Colarusso, Naples - Clinical Trials with Thioctic Acid.

The widest field of application for thioctic acid are hepatopathies from hepatitis to cirrhosis of the liver. In cardiac patients diuresis is favorably influenced. Surprising results were seen following infusions of 20 to 40 mg. of thioctic acid dissolved in isotonic sodium chloride solution given over a period of 5 to 6 hours. Until now 28 hepatic cases were treated with the Italian drug, among them 10 cirrhoses of the liver. All toxico-dyspeptic symptoms subsided. By improving the function of the liver parenchyma the symptomatology of the diseases is favorably influenced. Due to the diuretic effect, ascites and edemas are being eliminated. The icterus disappears. Furthermore, cardiac and pulmonary congestions respond well and the effect of strophantine is being improved. A certain cytostatic effect in leukemias could be seen following high doses. The leukocyte counts dropped from 39,000 to 9,000. Thioctic acid has an antitoxic action and is a liver protection factor.

6. Dr. Rausch - Clinical Activity of Thioctic Acid.

In a survey Dr. Rausch reported on his experiences so far obtained. We shall receive a copy of his manuscript. He also made statements on a control trial with placebos which is now being carried out. It has been revealed by these trials that there is a significant difference in the effect of thioctic acid and physiological sodium chloride solution. The blood count of the patients is favorably influenced by small doses. Leukocyte and thrombocyte counts increase.

Following points were considered in the discussion:

Thioctic acid leads to a decrease of the blood glucose via an effect on pyruvic acid and lactic acid. There is no influence on the functional test of the liver. Trials on the pyruvic acid metabolism revealed an initial increase and subsequent drop of the pyruvic acid values in the blood. The effect of high doses on leukemia persists for about 2 to 3 weeks.