November 28, 1947

Dr. C. R. Bickerton Blackburn,
Bard Hall, Box 184,
50 Haven Avenue,
New York City 32.

Dear Dr. Blackburn:

I am glad, indeed, to hear from you, having learned from the London office of Associated Ethyl Company Limited, and also from Dr. Fairley, of your being in this country. I had intended getting in touch with you, so that you might know that we shall be very pleased to have you visit us, and so as, also, to have an opportunity to discuss with you the cases referred to in your paper. I had a rather complete report on these cases some weeks ago, and I felt it necessary to write to the London office and to Dr. Fairley at once concerning them. Finding that you were to be here, I cannot but feel that it is important that we see you and present our views on this subject. Whether you hear from Australia or not, promptly, I wish to assure you that you are fully authorized to visit Cincinnati for the purpose of consulting with us on this and other problems which are of concern to Associated Ethyl. A number of the technical and medical representatives of the Company have been sent to this country and to Cincinnati at Company expense, for the purpose of an exchange of information, and it would be most unfortunate if you were not to do so if you can find the time during your stay. For our part, we shall welcome you and will undertake to make your visit worth your while.

Now as to the paper, I should prefer to leave its disposition until such a time as we can discuss the situation fully. I personally, believe, and have so expressed myself to Dr. Fairley, that your use of B.A.L. in these cases was without noteworthy effect upon the clinical outcome. The background of this opinion will require more evidence than I can put in a brief letter, but we have had occasion to study the effects of B.A.L. in a series of cases of lead, mercury, arsenic and other metallic poisoning, and we have also treated quite a number of cases of tetraethyl lead poisoning - not with B.A.L., but by other means. The course of the cases described by yourself was in no wise unusual, nor was recovery in any way remarkable. Certain other aspects of the problem have changed somewhat with the years and on the basis of experience, and therefore we should be reluctant to sponsor the appearance of an article which might well result in controversy, and which would fail in some respects to present what is now known on this subject.

I send you herewith one brief article, the only one we have published, to date, on B.A.L. It will serve to present only one aspect of our observations. Certainly it will show why the analytical findings in your cases may have been rendered somewhat erratic by the administration of B.A.L. We should be disposed to feel that one should go very slowly

indeed in recommending the use of B.A.L. in the therapy of tetraethyl lead poisoning. I am frank to say that I should entertain very serious reservations concerning its use, even experimentally, in any case of tetraethyl lead poisoning if I had any considerable doubt as to the likelihood of the survival of the patient. Your experience leaves me somewhat less fearful on this score, but I still have some concern as to the possible effects of its use.

I shall retain your manuscript until I hear from you further, in the hope that we shall have an opportunity to go over it together in some detail. I sincerely trust that your stay in this country will be interesting and profitable, and that we shall have an opportunity to share some portion of it with you.

Sincerely yours,

Robert A. Kehoe, M. D.

RAK ef

Enc.

Dr C.R.Bickerton Blackburn,
Bard Hall, Box 184
50 Haven Avenue,
New York 32, N.Y.

21 November 47

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

Dear Dr Kehoe,

I am writing to you on the advice of Dr R.Loeb and Dr A.Gilman of the College of Physicians and Surgeons, Columbia University, New York, where I am at present. I have a Rockefeller Foundation grant for about a year.

I enclose a draft paper on the treatment of TEL poisoning with BAL. I was fortunate enough to treat two men poisoned with TEL as I am the medical adviser to the Ethyl Company in N.S.W., Australia, and both men recovered. At the time I treated them I had seen no reference to the efficacy, or otherwise, of BAL in the treatment of lead poisoning but since then have heard very conflicting opinions. It was difficult to avoid the conclusion that BAL had been effective in the treatment of at least one of my patients.

I would appreciate your advice concerning the desirability of reporting these two cases and, if it is desirable to report them, to whom I should submit the report for publication. I am aware that much more should have been done concerning the lead excretion studies and that the method of estimating the lead in the urine was probably quite inadequate - circumstances precluded a fuller study.

The Ethyl Company has asked me to visit Cincinnati while I am over here and I propose to do this as soon as I can - probably in a few months time. So far the request has been verbal so I will wait for more definite instructions.

I hope my request does not cause you too much inconvenience,

yours sincerely,

C R Bickerton Blackburn

TETRA-ETHYL LEAD POISONING TREATED WITH BAL

(2:3-dimercaptopropanol, British Anti-Lewisite.)

C. R. Bickerton Blackburn M.D., M.R.C.P., M.R.A.C.P.

TETRA-ETHYL LEAD POISONING TREATED WITH BAL (2:3-dimercaptopropanol, British Anti-Lewisite).

C. R. Bickerton Blackburn M.D., M.R.C.P., M.R.A.C.P.

Tetra-ethyl lead is a colourless and somewhat volatile liquid used as an "anti-knock" in gasoline. It is insoluble in water but miscible with fats in all proportions. In the presence of sunlight it may decompose to triethyl lead compounds which are water soluble.[1, 2.] Motor and aviation fuels may contain up to 3 ml. of tetra-ethyl lead per gallon without their vapours being toxic to man or experimental animals.[3.]

Poisoning has most often been reported in men engaged in blending gasoline or cleaning out storage tanks that have contained leaded gasoline for some time, absorption taking place either by the respiratory tract or by the skin, through both of which tetra-ethyl lead easily passes. Storage tanks are especially dangerous for tetra-ethyl lead may be present in relatively large amounts in the "scale" on the tank walls or in the inevitable "sludge" on the floor of the tank. Cleaning operations lead to liberation of vapours from the "scale" or "sludge".[4.]

The toxic effects following absorption of tetra-ethyl lead are due to the lead content and are, fundamentally, precisely the same as those of poisoning with inorganic lead compounds. Absorption of tetra-ethyl lead into the circulation is somewhat delayed in the lung and skin but after leaving the circulation it tends to reach relatively high concentrations in fatty tissues such as the brain, liver and subcutaneous fat. Subsequently the organic lead compound decomposes into inorganic salts which produce the

oxic effects on the body cells, and especially the cells of the central nervous system where there may be a high lead concentration. During a period of 3 to 14 days after absorption the lead content of the various tissues becomes redistributed so that its distribution is ultimately the same as that following the absorption of inorganic lead compounds.[5, 6.]

The clinical features of tetra-ethyl lead poisoning are characteristically those of an acute encephalopathy occurring after a latent period which will vary inversely with the degree of exposure.[1, 2, 7.] Detailed descriptions have been given of the clinical features in articles reviewing up to 78 cases of poisoning and in this report only brief reference will be made to the typical features.

Within a few hours of exposure the subject develops increasing insomnia, weakness, restlessness, anorexia and tremors of his hands. If the exposure has been considerable there may be varying psychic changes, and, of these, excitement and mania are commonest. Wild and terrifying dreams, hallucinations, disorientation, physical activity and convulsions may herald an attack of acute mania. Other subjects may appear schizophrenic. Characteristically there is a slow pulse rate, a normal or subnormal temperature, a low blood pressure, little or no change in the erythrocytes, and a tendency to diarrhoea rather than constipation. Colic may occur but is not characteristic, general muscle pains are common but neuritic phenomena are not seen. The condition is an acute lead encephelopathy and the usual signs of chronic lead poisoning do not occur.

When severe symptoms become evident they do not disappear completely until recovery is ensuing - the general symptoms continue to progress and there are no true remissions and relapses.[2.] It is stated that those cases

with severe mania, requiring restraint, are "almost uniformly fatal".[1.] Treatment has consisted of sedation, fluids, and maintaining the urine alkaline to favour the excretion of lead or its deposition in bones. Hypertonic solutions were often given to combat cerebral oedema.

2:3-dimercaptopropanol, or BAL (British Anti-Lewisite) was introduced by Peters et al.[8.] as an effective antidote to Lewisite. Subsequent investigations have shewn that BAL is an effective antidote against poisoning with arsenic,[9,10,11.] mercury,[12,13.] gold[14,15,16.] and bismuth. In vitro, it will combine with iron, lead, tin, copper, cobalt, nickel, selenium, and antimony producing coloured and mostly insoluble compounds. BAL acts as an antidote to metallic poisons by forming stable compounds with the metals by virtue of its own two thiol groups and thus preventing them from combining with essential thiol compounds in enzyme systems and so producing their toxic effects. The stability and non-dissociability of the BAL-metal compounds prevents them from being toxic.[8,17,18,19.]

Two men, who were exposed to tetra-ethyl lead, and its derivatives, while they were cleaning out an aviation gasoline storage tank, developed typical signs of lead encephalopathy. One had mild symptoms but the other had convulsions and became maniacal. Both were treated in Royal Prince Alfred Hospital, Sydney, with BAL and made complete recoveries.

BAL was used for the treatment of these two men as it was considered possible that as lead is so closely related, chemically, to gold its toxic effects might similarly be counteracted. The possibility of BAL forming an insoluble compound with the lead in the tissues was considered but was thought to be of less importance than the prevention of irreversible changes

in the central nervous system.

CASE HISTORIES.

CASE I. R.K. a married storeman aged 30 years was admitted to Royal Prince Alfred Hospital at 12.30 a.m. on 23rd June.

On the 19th June he had commenced to clean out a storage petrol tank that had contained aviation spirit some 2 years previously but recently had contained water. He proceeded to remove the "slime" from the walls and internal "fins" using a piece of timber, held in his bare hands, as a scraper and during this cleaning process he acquired a number of minor abrasions on both hands. He wore rubber knee boots but no respirator and though "the fumes were dreadful", he spent between 6 and 8 hours in the tank. Before eating his lunch he washed his hands in soap and water.

On the morning of 20th June, having slept very poorly the previous night, he felt tired, "off-colour" and had some anorexia, but continued to clean the tank. He spent half the working day, wearing neither gloves nor respirator, on the floor of the tank scooping up the sludge with a tin and then pouring it into a bucket. One man filled the bucket on the floor of the tank while the other hauled up the full bucket and disposed of the contained sludge. Each 10-20 minutes the two men would change their jobs as the "fumes in the tank were so bad". He slept very little that night and had terrifying dreams, his appetite was non-existent, and he felt ill.

On 21st June he "felt awful", had diarrhoea, marked nausea, and some epigastric pains. He was weak and noticed an aching pain in his

upper and lower jaws. He was admitted to the local hospital with a diagnosis of a gastro-intestinal upset which was very prevalent in the town at the time.

After admission his intestinal symptoms settled down and within a day his diarrhoea had ceased, but he still had marked anorexia. He noticed a peculiar sensation in his hands - he continually wanted to rub them together. On the morning of 22nd June he was a little confused and in the early afternoon had a clonic fit during which he was unconscious. Recovering from his fit he was more confused and very restless. He was sent by ambulance to Royal Prince Alfred Hospital where on admission he could not clearly recollect the above detailed events.

There were no relevant facts elicited in his past or personal history.

On Examination: He was a young man who writhed on the bed making curious stretching movements of his limbs and back and continuously rubbing his hands over his face. He seemed to be little interested in his surroundings. He tongue was dry and coated and his skin warm, dry and of normal colour. There were a number of superficial abrasions on the backs of both hands. He complained of pains all over his abdomen but there was no local tenderness. There was some tremor of his extended hands. His radial pulse was of good volume, regular and its rate was 64 per min; his arterial blood pressure was 120/55 mm of mercury and his oral temperature 98.4°F. His eyelids were widely separated so that he appeared to be exophthalmic but his

abnormalities were found on physical examination. His weight was 150 lbs.

Treatment and Progress: He was confined to bed and given sodium phenobarbitone and morphine sulphate. He was given 750 ml. saline with 5% glucose and 500 ml. sodium lactate solution intravenously. Subsequently sodium citrate was given orally in sufficient quantity to keep his urine neutral or alkaline to litmus. He received calcium lactate 10 grains three times a day and had been given parenteral calcium gluconate by his local practitioner before being sent to Sydney.

Treatment with BAL (a 10% solution of 2:3-dimercaptopropanol in peanut oil with 10% benzyl benzoate) was commenced at 2.30 a.m. when 4.4 mg/kg (1 ml. per 50 lbs) were given by intramuscular injection into his buttock. Subsequently 4.4 mg/kg were injected each four hours for 3 doses then 2.2 mg/kg were given twice daily from 23rd June to 27th June. His only reaction to BAL was that he said the smell put him off his food.

On the morning of the 23rd June he still appeared to be exophthalmic; his tongue was clean and he was "dopey", but by mid-day he had greatly improved. He was then much clearer mentally and was taking some food as well as fluids by mouth. He stated that his jaws were still sore and that his muscle pains, though present, were less severe. He felt tired but was unable to sleep without sedatives.

On the following day he looked better, but had cramps in his calves which were a little tender, and he was very restless and active in bed. He was refusing all food for he said it tasted of BAL. His eyes were "dry and sore". He had no diarrhoea or vomiting.

During the next two days his condition generally improved and he began to eat more food. He had some headache, was still excessively alert, his pupils were dilated, and he appeared to be exophthalmic. Considerable difficulty was experienced in inducing sleep. He complained of some local pain following his BAL injections and vomited once.

On the 27th June he was very restless and mentally active in the early morning, but towards mid-day became unstable, refused treatment and commenced walking around in the ward. At 12.15 p.m. he became hypopmanic and escaped into the street for a few minutes. He was returned, with persuasion, to the ward and given morphine sulphate, hyoscine hydrobromide and BAL 4.4 mg/kg at 1.10 p.m. His mental condition was confused, excited and deluded.

At 1.30 p.m. he had an epileptiform fit with typical clonic and tonic phases and involuntary micturition. Following his "fit" he was hallucinated, disorientated and tended to become violent. He tore up his pyjamas and frustrated an attempt to give him hypertonic glucose intravenously after some 250 ml. had been given. In spite of large doses of hyoscine hydrobromide, Dial and sodium phenobarbitone his psychomotor activity was little abated though he was less violent. At 7.30 p.m. he passed urine into his bed. BAL was given in 4.4 mg/kg doses at 1.10 p.m., 4.30 p.m. and 8.50 p.m. but he as very restless and confused and was only partly controlled with four hourly hyoscine hydrobromide.

On the 28th June he continued to be hallucinated, deluded and disorientated. He was quite irrational - laughing and talking to

himself whilst prowling round the room, and was most uncooperative. He was somewhat quietened with Nembutal and slept during the later part of the night. BAL in doses of 4.4 mg/kg was given at 2.30 a.m. and 6.30 a.m. and 3.2 mg/kg at 8.30 p.m.

By the next day he had greatly improved - he could talk rationally for brief periods, was more cooperative and, assisted with Nembutal, slept most of the day. He received BAL 4.4 mg/kg at 6 a.m. and 6 p.m. each day until 3rd July.

On 30th June he was very much improved, was quiet all day, and only required sedation at night.

Between 29th June and 3rd July his mental condition improved and was normal except for insomnia, unpleasant dreams which were still very troublesome, and restlessness. He felt "dopey" most of the time on account of the Nembutal he was receiving. He increasingly complained of muscle pains which made him want to stretch continuously, but by 3rd July, these movements caused so much pain that he could only sit up with considerable difficulty. During this time he had some abdominal colic with frequent bowel actions (approximately three per day).

On 3rd July his tongue was dry and dirty and he did not look so well. He was given BAL 4.4 mg/kg fourth hourly beginning at 6 p.m.

By 4th July he felt better and he could obviously move with much less discomfort and his abdominal pains had abated. His optic discs and fundi were normal. BAL 4.4 mg/kg fourth hourly was

continued till 10.30 p.m. when, in error, he received a dose of 8.8 mg/kg. He developed a marked reaction with parasthesiae of his limbs, face and mouth; he was giddy, prostrated and dyspnoeic, and had a constrictive pain in his chest. His arterial blood pressure rose to 190/130 mm of mercury. These symptoms were transient and by the next morning he was feeling much improved over his condition of the previous morning - his muscle pains were less, he felt better and he had less abdominal discomfort. All the symptoms that had occurred the previous night had vanished.

From the 5th to 14th July his progress was steady and only interrupted by the development of a mild infection in one buttock which rapidly responded to Sulphadiazine.

On the 7th July he developed a rash which was erythematous and macular on the arm and legs, but finely papular on the palms and soles. All his pains vanished, he became mentally quite normal, and he required diminishing amounts of sedation each night. After 10th July he had nausea, often with vomiting, after each injection of BAL.

From 5th to 13th July he received 2.9 mg/kg BAL eight hourly and from 14th to 21st July 1.5 mg/kg twice a day.

Blood pressure readings were usually between 150-200/100-110 mm of mercury depending on how recently BAL had been given, but by the 14th July his blood pressure was 125/60 mm of mercury. His pulse rate ranged between 48 and 66 per minute during the first five days in hospital, during the next week between 60 and 75 per minute,

and after 5th July between 70 and 90 per minute. His oral temperature varied between 96.8°F and 98.4°F during the first ten days after admission but the majority of readings were below 98°F.

Until the 28th July his sleep was always interrupted by dreams which gradually lost their unpleasant character and on discharge from hospital on 30th July he was sleeping and dreaming normally. His rash disappeared rapidly after ceasing BAL administration.

Laboratory Data.

1. Daily excretion of lead in the urine:

Date	Number of days since first exposure to lead	Urine lead content (mg per 24 hours)	Urine volume (mls per 24 hours)
23/6	4	0.00	37 (admission specimen)
24/6	5	0.30	
28/6	9	0.11	(incomplete)
2/7	13	0.13	2500
4/7	15	0.12	2380
5/7	16	0.08	2400
6/7	17	0.03	
7/7	18	0.03	
9/7	20	trace	

2. Blood Counts:

23/6 Haemoglobin concentration 14.5 gramme per 100 ml.; very occasional stippled red blood cell seen; total leucocytes 14,100 per c.mm. of which 81% were neutrophil granulocytes.

9/7 Haemoglobin concentration 13.7 gramme per 100 ml.; no stippled red blood cells seen; total leucocytes 7800 per c.mm. of which 77% were neutrophil granulocytes.

CASE II. T.J., aged 34, a married storeman-driver with two children, was admitted to Royal Prince Alfred Hospital at 10.30 p.m. on 22nd June.

On 20th June he had assisted R.K. in the collection and disposal of the sludge on the floor of the tank already described. He wore protective rubber knee boots, canvas gloves, but no respirator was worn. He also noticed that the "fumes" were very bad inside the tank.

He developed marked insomnia, anorexia, and a "sickly feeling in the stomach" on the evening of 20th June and these symptoms had increased until his admission to hospital. He had mild diarrhoea for a "few" days, which had ceased on arrival in Sydney. On admission he felt very tired but apart from slight headache and tremor of his hands, which had been present for one day, he had no other symptoms.

He attributed his initial gastro-intestinal symptoms to "food-poisoning", which was prevalent at this time in the Hotel in which he was staying, but the development of insomnia and tremors with marked anorexia caused him to consult a doctor.

Neither his past nor his personal history revealed any relevant facts.

On Examination: He was a rather worried, ruddy-faced, red-haired young man. His skin was warm and dry, his pupils appeared to be somewhat dilated but were otherwise normal, and apart from evidence of lack of sleep he appeared well. He had a moderate tremor of both hands. His arterial blood pressure was

120/75 mm of mercury, pulse rate 66 per min, and his oral temperature 96°F. There were no other abnormal physical signs. His weight was 125 lbs.

Treatment and Progress: He was confined to bed and given barbitone sedation. His urine was kept neutral or alkaline in reaction by oral potassium citrate; sufficient fluids were administered to keep his urine volume up to or over 2 litres per diem, and calcium lactate was given by mouth.

BAL (10% 2:3-dimercaptopropanol in peanut oil with 10% benzyl benzoate) was given intramuscularly into the buttocks each four hours, commencing at 12.15 a.m. on 23rd June, for four doses which were 4.4 mg/kg, 3.5 mg/kg, 4.4 mg/kg and 3.5 mg/kg respectively. Following the first injection there was a moderate reaction - he shivered, felt giddy and then sweated; he felt nauseated, had some muscle pains, and he had pain in his abdomen and at the site of the injection. Reactions characterised by nausea and vomiting, and usually with pains in his ears accompanied the next three injections of BAL - in each instance coming on some 15-30 minutes after the injection.

On the day following admission his anorexia diminished and he began to eat well.

At 9.30 p.m. on this day he had 2.2 mg/kg of BAL injected into his buttock and this dose was subsequently given at 9.30 each morning and evening during the next four days. He continued to have pain in his buttock and ears following each injection.

In the evening of the 25th June he became very "bright" and complained of some headache. As his restlessness, which had been present since admission was increasing, he was given morphine sulphate in the evening. He had not slept well since admission in spite of barbitone sedation, and it had been noticed that his palpebral fissures were widened so that he appeared exophthalmic. His pupils were considerably dilated during this period.

On the morning and afternoon of the 27th he became very restless and upset about his friend (Case I), and for a while he was most uncooperative. However, he responded to increased sedation with phenobarbitone and slept well. As he was rather restless and unwilling to stay in bed during the following three days, he was kept heavily sedated with phenobarbitone. BAL 3.9 mg/kg was given 6 hourly on 28th June, 1.9 mg/kg 6 hourly on 29th June and from 30th June to 3rd July 3.9 mg/kg was given twice daily. From the 30th June onwards his improvement was continuous; his eyes became normal and lost their exophthalmic appearance, his pupils contracted, he became a quiet and most amenable man, and, apart from a minor infection in the left buttock (rapidly cured with Sulphadiazine) he made an uninterrupted recovery. The dosage of BAL was reduced to 1.9 mg/kg twice daily on 4th July and to 1.9 mg/kg daily on 11th July; he received his last dose on 14th July.

His arterial blood pressure was 120/75 mm of mercury on 29th June and 140/80 mm of mercury on 14th July. His fundi were reported to be normal on 4th July.

During the first five days after admission his pulse rate

ranged between 52 and 60 per minute with but three readings over 60; his oral temperature ranged between 97 and 98°F for the most part.

Laboratory findings:

1. Daily excretion of lead in the urine:

Date	Days since exposure	Content of lead in mg. per 24 hours.	Urine volume in ml.
24th June	4	0.09	
26th June	6	0.09	
27-28th June	8	0.79	
28-29th June	9	0.50	3640
30-1st July	11	0.45	4340
2-3rd July	13	0.24	3450
4-5th July	15	0.03	
5-6th July	16	trace	1050
7-7th July	17	trace	

2. Blood Counts:

23rd June Red blood cells 5.67 million per c.mm.; haemoglobin concentration 17.2 gramme per 100 ml.; total leucocytes 11,000 per c.mm., neutrophil granulocytes 90%. No stippled cells were seen.

DISCUSSION.

There is no question that both these men were suffering from the effects of tetra-ethyl lead absorption, and that the route of absorption was both the lungs and the skin. Though both men had changing amounts of lead in their urine specimens it was interesting to note that more lead was found in the urine from T.J. (Case II) than in the urine from R.K. (Case I) who was more seriously affected and had much greater exposure. The excretion of lead in the urine is variable, and, in the experimental animal and man, there is usually more excreted by the bowel than by the kidney after the absorption of tetra-ethyl lead.[1,2,20,21] It is also

possible that therapy with BAL affects the amount of lead recovered from urine as either the compound of BAL and lead may be relatively insoluble and therefore not appreciably excreted, or the method used[22.] for the estimation of the lead content in the urine may not be adequate for the detection of BAL-lead compounds. In view of the limitations of the adsorption method of estimating lead in the urine and considering that R.K. (Case I) received much larger doses of BAL than did T.J. (Case II) it seems more likely that the amounts of lead recovered were not true indications of the amounts actually present and that the BAL-lead compound was not recovered completely by this method.

The intoxication in T.J. (Case II) was relatively mild when compared with that of R.K. (Case I) who was seriously ill following much greater exposure. As the clinical features of the two men were parallel the discussion will largely centre round the more seriously affected man.

The clinical features of both men were typically those following the absorption of tetra-ethyl lead. In R.K. (Case I) minor symptoms appeared a few hours after exposure but within 48 hours serious symptoms were present - the early development of confusion, restlessness and of an epileptiform attack indicated massive absorption of tetra-ethyl lead.

R.K.'s illness was atypical in that his severe symptoms almost completely remitted, after some 16 hours of treatment, for 4 days during which he felt well. These symptoms returned with increased severity and he became maniacal, tried to escape and had another epileptiform attack. These severe symptoms remitted after 2 days of treatment but he remained well for only 4 days before symptoms were again remarked. On this occasion his symptoms were not related to the central nervous system but to his

general musculature and abdomen. Such definite remissions of severe symptoms do not characteristically occur in subjects with tetra-ethyl lead poisoning.

Both of the remissions mentioned above and the final abolition of the last recrudescence closely followed the administration of large doses of BAL. Furthermore, each recurrence followed within 4 days of the reduction of the dose of BAL to a maintenance level. The patient himself was most insistent that BAL relieved his muscle pains and abdominal discomfort in his last recrudescence.

It is suggested that the course of the intoxication in R.K. (Case I) was as follows: tetra-ethyl lead, absorbed from the lungs and skin, become relatively concentrated in the central nervous system and, when the organic compound broke down to inorganic lead salts, symptoms were produced; on the administration of BAL a non-toxic compound was formed which was, perhaps, relatively insoluble; with reduction of the dose of BAL either some of the non-toxic BAL-lead compound was broken up freeing inorganic lead, or else tetra-ethyl lead still present in the organic state continued to be converted to toxic inorganic lead; in either or both instances there were inadequate amounts of BAL present to render the lead non-toxic and symptoms again occurred; further administration of large doses of BAL again had a full antidotal effect but reduction in dosage once more resulted in the recurrence of symptoms; these last symptoms were probably due to lead distributed throughout the organism as sufficient time had now elapsed for this to occur; once more

adequate dosage of BAL had a full antidotal effect.

It is difficult to avoid the conclusion that BAL was the active agent in the production of remissions, especially as other therapy did not change apart from some variation in the dosage of sedatives.

A large amount of BAL was given to R.K. (Case I) who received some 16 grammes in all. It is considered, nevertheless, that larger doses should have been given for a longer period of time in the early stages of his intoxication. It has been reported that for the relief of encephalopathy from mercuy poisoning far higher doses are required than for other forms of mercury intoxication and a similar set of circumstances may prevail in lead intoxication.

It seems important to stress the apparent need for continued high doses of BAL in acute lead encephalopathy - smaller doses may lead to failure and, it is possible, to ill effects. Some arsenical compounds when combined with 1 mol of BAL have been found to be more toxic than the original arsenical compound, though 2 mols of BAL render them non-toxic.[23.] It appears that full doses of BAL (4.4 mg/kg) should be given each 4 hours till all symptoms have subsided and then doses of 4.4 mg/kg given three times a day for another 14 days before ceasing its administration. Treatment should be instituted immediately exposure to toxic concentrations of tetra-ethyl lead has taken place.

Toxic effects from BAL occurred in both men, mildy in T.J. and limited to some local pain at the site of injection and an earache following each injection of 4.4 mg/kg. R.K. (Case I), on the other hand, shewed both acute and chronic toxicity. On the evening of the 12th day of treatment he received, in error, 8.8 mg/kg in one dose and rapidly developed prostration,

a constrictive feeling in his chest, dyspnoea, limb and oral paraesthesiae, and a feeling that "he had no nose". His blood pressure rose to 190/130 mm of mercury at this time. These symptoms were transient and had all cleared by the next day when he felt much improved. On the 15th day of BAL administration he developed a typical drug rash - he had a maculo-erythematous rash on his forearms, arms, thighs and legs which was mainly on the dorsal surfaces and a papular rash on both palms and soles. Itching was quite marked. The rash rapidly disappeared on cessation of BAL injections.

SUMMARY.

1. Two men suffering from tetra-ethyl lead poisoning have been reported.
2. Both men were treated with 2:3-dimercaptopropanol (BAL or British Anti-Lewisite) and made full recoveries.
3. Continued high dosage of 2:3-dimercaptopropanol (4.4 mg/kg administered as a 10% solution in peanut oil with 10% benzyl benzoate intramuscularly each 4 hours) was necessary to produce a complete antidotal effect.
4. Acute and chronic toxic phenomena followed the administration of the 2:3-dimercaptopropanol solution in both men but were not serious in either.

My thanks are due to Dr. E.M.A. Day, Biochemist in the Fairfax Institute of Pathology, Royal Prince Alfred Hospital, for the estimations of the concentration of lead in the urine specimens.

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