Influence of Dithiopropanol (BAL) on Human Lead Metabolism

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Barron and Kalnitsky (*2*) have shown that certain heavy metals, including lead, may produce complete inhibition of the sulfhydryl-containing enzyme, succinoxidase, and that the enzyme is reactivated on the addition of certain dithiopropanol (BAL) derivatives. This is the type of evidence that has been accumulating in support of the hypothesis that heavy metals are toxic to biological systems because of their reversible combination with the sulfhydryl groups of the protein fraction of cellular enzymes (*4*). The value of dithiopropanol in the treatment of rabbits poisoned by single and multiple intraperitoneal inoculations of lead nitrate has been examined by Braun, Lusky, and Calvery (*3*). Their experimental findings were regarded by themselves as evidence that lead and dithiopropanol exert additive toxic effects in both acute and chronic types of poisoning due to lead.

We have studied the effect of one intramuscular dose of dithiopropanol (5 mg./kg. of body weight) upon the concentrations of lead in the blood and urine of each of a series of men whose occupations, at the time of the observations and for some time previously, involved no exposure to lead or varying degrees of severity of exposure. Some of these men were suffering from lead poisoning, and others were not. The observations were carried out, repeatedly, upon a number of the men. Samples of blood and urine were analyzed for lead by a dithizone method (*1*) of known sensitivity and precision.

The concentration of lead in the whole blood decreases promptly and considerably following the administration of this agent (Table 1). The initial rate of decrease is extremely rapid, a sizable change being demonstrable within 7½ minutes, and, judging from the apparent hyperbolic relationship of the early values, being well under way even earlier. The fall appears to reach its maximum within 8 hours; it is relatively greater, but absolutely less, the lower the initial concentration of lead in the blood. The concentration in the blood returns to approximately the previous level within 24–48 hours. This entire series of effects can be obtained again and again by repetitive administration of the agent.

The concentration of lead in the urine has been found to be moderately or greatly enhanced by the administration of dithiopropanol (Table 1). The urinary concentration of lead reaches its peak within an hour or two following the injection and diminishes rapidly to the previous level in from 8 to 24 hours. In those cases in which the increase in the concentration of lead in the urine was of only moderate proportions, the analysis of blood samples, drawn at the end of the functional periods represented by the samples of urine, demonstrated that the usual response to the administration of dithiopropanol had occurred therein, and the usual symptomatic effects, if any, of the agent were observed.

The concentration of lead in the blood plasma of these men was found to be independent of the cellular concentration of lead and was also unrelated to signs or symptoms of lead intoxication. It appeared to be unaffected by the administration of the agent (Table 1). The samples of plasma, which averaged 25 grams in weight, were obtained by the prompt centrifugation of whole blood drawn into a dry syringe and heparinized. The observations on the concentration of lead in the plasma cover the extremes in the range of cellular concentration of lead. These results indicate that relatively large quantities of lead released from the erythrocytes do not remain within the blood stream, but are lost with great rapidity, to appear, presumably, in the tissues generally as well

TABLE 1

CONCENTRATION OF LEAD (μg./100 GRAMS) FOLLOWING INTRAMUSCULAR ADMINISTRATION OF DITHIOPROPANOL (BAL)

Subject	Date	Before BAL			Seven minutes after BAL			One hour after BAL		
		Cells	Plasma	Urine	Cells	Plasma	Urine	Cells	Plasma	Urine
C. F.	12–31*			2						160
	2–3	70	9	3	40	6		28†	7†	9†
W. E.	12–25*			2						35
	2–10	65	9	1				40	12	48
E. G.	12–10‡	200	9	16				130	9	250
	12–27	145	5	9						580
N. B.	1–30‡	340	5	75	290	8				1,760§
	2–10	240	6	24	200	10				520§
A. E.	1–31‡			17						620
	2–11	315	8	11	230	14				430
O. C.	1–31‡			18						51
	2–17			36						1,310§
J. H.	3–25‖	1,250	6	11	1,250	6				23
	3–28	1,100	3	14	1,200	3		1,050	3	113§

* Case of poisoning with bichloride of mercury.

† Samples taken ½ hour after administration of BAL.

‡ Subject suffering from lead colic on this date, but not on that of later observation.

§ Samples taken 2 hours after administration of BAL.

‖ Subject not suffering from lead colic on either occasion. He was given 1.8 mg. of dithiopropanol/kg. of body weight on each occasion; the other men were given 5.0 mg./kg.

as in the urine. They also suggest that a great proportion of the lead remaining in the plasma is bound to some constituent or radical that is fully saturated thereby, even when the lead concentration in the whole blood does not exceed the normal limits. These facts and considerations may well explain our inability at any time to confirm the reports of Smith, Rathmell, and Marcil (*5*), to the effect that the lead concentration in the plasma is elevated in human lead intoxication.

The interest that attaches to any agent that can produce such remarkable metabolic effects as those described above is naturally great. By carefully designed metabolic experiments, we have been unable to discover evidence of the ability of any other therapeutic agent or combination of agents to influence materially the pattern of lead metabolism in the human organism. The administration of acids, alkaline salts, and iodides, as well as experimentally induced changes in the calcium and phosphorus metabolism, has failed utterly in our hands to bring about more than the most dubious and insignificant alterations in the lead content of the blood or in the rate of excretion of lead on the part of normal individuals or of persons with considerably increased quantities of lead in their tissues and excreta. Indeed, we have found no effect which could not be brought about more strikingly and more persistently by altering the rate of water intake of the patient or subject under study.

Thus, the effects of the administration of dithiopropanol are unique in our experience and are of potentially great physiological importance. However, their significance at this time should not lightly be credited to the field of therapy, since the intensity and brevity of the single response is such that no quantitatively important proportion of the absorbed lead of a poisoned or endangered individual has been removed thereby from the body.

We also wish to emphasize that dithiopropanol is potentially a dangerous drug, and that lead intoxication is largely a self-limited disease for which the only primary treatment of proved value is the removal of affected men from further exposure to lead. We have been unable consistently to shorten the clinical course of lead intoxication, to maintain a significantly increased rate of elimination of lead, or to decrease the duration of the occupational disability of affected men, by repeated doses of the drug, because of the induction of hypertension, annoying local or generalized immediate reactions, or delayed generalized muscular aching. In addition, our observations suggest that the drug may have relatively less effect, the greater the concentration of lead in the body fluids. This phenomenon is analogous to the observations of Barron and Kalnitsky on the disproportionate reduction of the effectiveness of dithiols following increases in concentration of the heavy metal inhibiting preparations of succinoxidase.

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The Ultraviolet Absorption Spectrum of Cerebrospinal Fluid: Ascorbic Versus Nucleic Acid

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A recent report (*8*) on the origin of an enzyme in cerebrospinal fluid (CSF) which produces a chromatolytic effect following cerebral concussion has been predicated upon spectrophotometric data based upon two assumptions which, according to our experiments, are not valid. These two assumptions are: (1) "Normal" CSF (of humans and dogs) has a relatively weak and characterless, so-called "S-shaped" ultraviolet absorption spectrum; and (2) "abnormal"[1] CSF's differ from "normals" by showing a strong and characteristic absorption spectrum with band peak at 265 mμ, which Spiegel, *et al.* (*10, 11*) and others (*1*) have attributed to nucleic acids.

We have been carrying on a systematic study of the ultraviolet absorption of the CSF since February 1946 and have analyzed[2] to date the CSF's of 80 humans, 5 dogs, and 12 cats. Contrary to the widely accepted assumptions stated above, we have found that the same strong 265-mμ band dominated the spectrum of the "normal" as well as of the "abnormal" CSF and was in either case due to ascorbic acid and not nucleic acid. In fact, no significant amount of nucleic acid has been found by us in either the "normal" CSF's of dogs, cats, or humans or in the "abnormal" CSF's of a large number of epileptic patients, a cocaine-convulsed dog, or 6 cats after cerebral concussion. The failure of Spiegel, *et al.*[3] and others (*5, 6, 9*) to observe the strong 265-mμ band in "normal" CSF has probably been responsible for the misinterpretation of the same band in the "abnormal" CSF. The weak "normal S-shaped" curve for CSF was described as early as 1927 (*5*) and unfortunately has been "confirmed" since by various investigators, with one exception (*7*). Strong sources of ultraviolet irradiation used in the measurement technique in earlier methods or other factors which destroy the easily oxidizable ascorbic acid readily explain the failure to observe its presence.

Our evidence for positively identifying the 265-mμ band in CSF with ascorbic acid has been derived from an extensive investigation (approximately 1,000 spectrophotometric curves have been analyzed) of the effects of a number of independent variables which affect its structure, and consequently the absorption spectrum, in characteristic fashion.

The unique qualitative and quantitative alterations of the spectrum of ascorbic acid when the pH is shifted and when different solvents are used (*14*) afford effective criteria for its identification. The effect of pH on ascorbic acid is pronounced, due to the marked difference in the spectrum of the ion and the undissociated molecule. When the pH of ascorbic acid in

[1] "Abnormal" fluids are defined as fluids associated with abnormal neurological conditions, namely, (1) convulsive states induced in dogs by electrical shock; (2) human cases with nervous disorders such as epileptic or other convulsive states (*9, 11*).

[2] A Model D. U. Beckman quartz spectrophotometer and cells with a path length of 1 cm. were used.

[3] The presence of a strong band at 265 mμ was observed (*11*) in two out of three "normal" cases but was discounted.