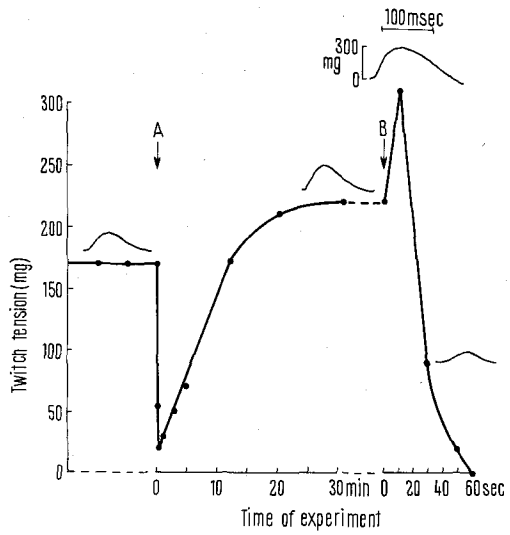

Fig. 1. Changes in twitch tension of single muscle fibre during loading with glycerol and at the beginning of its removal. The arrow A indicates the moment when R was changed for R+220 mM glycerol. The arrow B indicates the beginning of glycerol removal. Note the change in time scale from min to sec at the beginning of glycerol removal. Myogramms typical for different stage of experiment are shown close to corresponding points of the curve.

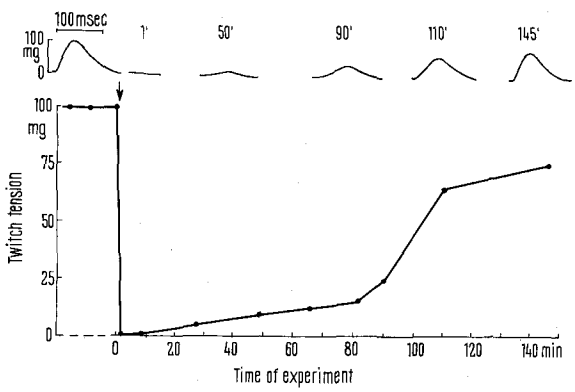

Fig. 2. Restoration of twitch tension after removal of 165 mM glycerol. The arrow indicates the moment when R+165 mM glycerol was changed for ordinary R. The figures besides the myogramms denote min of experiment when these samples were recorded.

Little by little the amplitude of isometric contractions increased, usually as S-shape curve and approached the constant level which was usually equal to, or a bit less than, the initial one (Figure 2).

The time course of twitch tension recovery varied considerably in experiments with the same glycerol concentration. For example, after the removal of 165 mM glycerol, the extreme values for halftime of twitch recovery were 12 and 200 min. In spite of this variability, there is no doubt that the recovery of twitches proceeded faster and easier after 110–132 mM glycerol than after 165–220 mM. In the former case, the complete restoration was accomplished for 20–60 min and in the latter it was delayed usually for several hours. In case of 400 mM glycerol, in accordance with other evidence[1,9], no restoration of isometric twitches was observed during 5–10 h of experiment, although in a few instances weak isotonic shortening appeared.

We considered the recovery of normal isometric twitches after glycerol removal as a result of restoration of normal connection between the T-tubules and surface membrane. However, the time course of twitch recovery, besides changes in the T-system, may reflect some other reversible alterations produced by glycerol efflux in muscle fibre, most probably, in its surface membrane.

ВЫВОДЫ. 1. Исчезновение одиночных изометрических сокращений, вызванное отмывкой 110–220 мM глицерина из изолированных мышечных волокон лягушки, носит обратимый характер. 2. На определенном этапе отмывки глицерина в ответ на одиночное электрическое раздражение возникают локальные сокращения волокна, распространяющиеся по волокну со скоростью порядка 3 мм/сек. 3. Выход глицерина резко повышает чувствительность волокна к механическим воздействиям и часто сопровождается развитием некроза.

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The LD_{50} Value of Tetraethyl Lead[1]

Ecologically speaking, lead is under attack. Among other things, it is regarded as the leading cause of childhood poisoning in the United States today[2,3]. Looking at the subject of lead from a different aspect, the Director-General of Research and Operations for the Canadian Food and Drug Directorate has indicated that an estimated 15 tons of lead enter the atmosphere over Los Angeles each day[4]. As most of this comes from the residue of burned, leaded gasoline, it seems worthwhile to closely examine the biological effects of some of the compounds involved. Tetraethyl lead was chosen as the starting point. This paper represents a preliminary report on the toxicity of this compound.

Although the literature revealed a minimal lethal dose for the intraperitoneal route of administration[5] and an

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approximate lethal dose for the oral route[6], there were no indications of an LD_{50} value (that dosage which will kill 50% of a test group of animals), nor of a dose response curve for oral doses. In order to determine what kinds of harmful effects to expect, and at what dosages they might be manifest, the decision was made to run experiments to assess both the LD_{50} value and the response curve. Due to the variations found in biologic entities, it is not generally considered meaningful to use the terms 'minimum lethal dose' or 'lethal dose' as once was customary. The aspect that is dealt with here is the LD_{50} value for single dose, oral administration.

Method. 16 Sprague-Dawley albino rats, 8 males and 8 females, were selected at random for these tests. The females ranged in weight from 150 to 250 g and the males varied from 350 to 425 g. In previous studies, a lowered resistance to Salmonellosis and chronic respiratory disease was noted. Consequently, stringent sanitary controls were put into effect and maintained during the experimental period. WEIL's[7] method of moving averages was the design utilized.

Procedure. The tetraethyl lead was obtained as a 98% pure solution from Ventor Corporation, Beverly, Massachusetts, USA. The lead compound was dissolved in 100% pure peanut oil to yield a concentration of 7.32 mg/ml. Each animal was weighed, the appropriate amount of solution was calculated and then pure oil was added to bring the volume administered up to 2 ml. Thus all animals received a similar dose of oil.

The animals were randomly assigned to 4 groups, except balancing was employed to assure an equal distribution of males and females in each group. Each of the groups was administered a different dosage level, with the logarithms of successive dosages differing by a constant (0.11394) according to the method set forth by WEIL[7]. Group I received a dose of 10.0 mg of compound per kg body weight, Group II received 13.0 mg/kg, Group III received 16.9 mg/kg and Group IV received 21.97 mg/kg. All doses were in a geometric progression with a factor of 1.3.

All animals were kept in the same light-cycled, temperature-controlled animals confinement room with their cages equally spaced on acceptable racks. 12-h light cycles were employed. Handling prior to the experimental period was restricted to one experimenter and no handling occurred between the administration time and time of death. The mortality data was collected over a predetermined, 14 day period of observation. The rats were visually examined daily for toxic signs, as well as for disease or parasites.

All dosages were administered by intragastric intubation of the 2 ml doses. Food and water were available in equal quantities to all groups. All rats were obtained from the supply house at a weight differential not to exceed $\pm$ 50 g. This was necessary in order to control for lead absorption differences due to amount of fatty tissue and to arrive at a narrow range of variance of dosages based on body weight. At no time during the 14 day period were the animals permitted to come into contact with sunlight or ultraviolet light, thus controlling for the highly variable absorptions of the compound from the blood serum which these factors may induce[8].

Results. The mortalities which resulted were 1 of 4 at 10.0 mg/kg, 0 of 4 at 13.0, 4 of 4 at 16.9 and 4 of 4 at 21.97. The mortality data was then matched to WEIL's tables. The following formula for computing the LD_{50} value was utilized: $LD_{50} = \log m \cong \log D_a + d(f+1)$ for $K = 3$. d was previously established as 0.11394 and the $\log D_a$ represents the log of the lowest of the four doses. Thus, with the f-value obtained from the tables, the LD_{50} value was found to be 14.18.

The estimation of the 95% confidence internal of this value is determined by the formula: $\sqrt{\log m} = d\sqrt{f}$. The LD_{50} and its confidence interval can thus be estimated as 14.18 (12.62 to 15.93) mg/kg. No curves are obtained using this method. It is planned to present these in a later paper.

Conclusions. All animals displayed neurological signs: lethargy, irritability and ataxia (muscular incoordination manifested when voluntary muscular activities are attempted) which represent an initial phase observed commencing with the second day. Violent jumping, trembling and thrashing following a loud noise plus aggressiveness and fighting appeared to represent a second stage in the progress of the toxicity. The aggressiveness was particularly manifest in Group III and IV males commencing with the fifth day. This was followed by convulsions, intermittent uncontrolled thrashing and, finally, death commencing with the sixth day. The three stages were observed in all groups (although death was not seen in one group) with the incipient stages appearing sooner and the progressive stages occurring faster in those animals receiving the higher doses.

Zusammenfassung. Im Hinblick auf den offensichtlichen Mangel eines LD_{50}-Wertes für Bleitetraethyl wurde bei intragastrischer Applikation im Rattenversuch der Wert 14,18 mg/kg (Spielraum 12,62–15,93) ermittelt.

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Enhancement of Anaphylaxis of Isolated Smooth Muscle by Adenosine Phosphates and Inhibition of Anaphylactic Mechanisms by Adenosine-3′,5′-Cyclic Monophosphate

Anti-anaphylactic effect of adrenalin was shown to involve inhibition of antigen-mediated histamine release[1,2]. Also, it has been shown that histamine release is suppressed by theophylline[3]. Since both catecholamines and methylxanthines have distinct positive action on adenosine-3′,5′-cyclic monophosphate (cyclic AMP) system, it was assumed that their inhibitory actions on histamine release might be due to an increase of cyclic AMP: Recently, evi-