

observed in only 4 dogs suffering from severe trichinosis. These animals (M12, M4, M9, M7) that received 32, 33, 40 and 66 thousand trichina larvae per kilogram of body weight exhibited increases in serum calcium, eosinophiles and total leucocytes. At the same time a moderate decrease was exhibited in the level of inorganic phosphate. Figs. 1 and 2 depict these changes as observed in M9. In contrast with these findings, M10, F13, and F5 had marked eosinophilia but no rise in calcium was observed although they received 34, 40, and 55 thousand larvae per kilogram of body weight. Fig. 3 graphically represents findings observed in F5 which are typical of these animals.

Summary. No significant changes in cell volume, total erythrocyte count and hemoglobin values were observed in trichina-infected dogs. All animals exhibited increases in eosinophiles which reached a maximum 10 to 15 days after infection. Significant increases in serum calcium, which reached a maximum (16-18 mg %) 11 to 18 days after infection, were observed in only 4 dogs. It would appear that hypercalcemia can only be elicited by a massive infection, whereas an eosinophilia will always result from ingestion of fewer organisms.

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Absorption of Drugs Through the Bone Marrow.

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For years the writer has been studying the penetration of drugs into the body through unusual channels and has published papers on their absorption through the bladder, urethra, ureters, vagina, eyes, ears, nose, pharynx, esophagus and pathological versus normal skin and mucous membranes.^{1, 2} Having observed that drugs penetrate the tooth pulp and canaliculae,³ the author determined to investigate what drugs and poisons in general can be absorbed through bone marrow and how rapidly. Such a research was deemed especially desirable because of the recent work of Morrison and Samwick⁴

¹ Macht, D. I., *J. A. M. A.*, 1938, **110**, 409.

² Macht, D. I., *Arch. internat. de Pharmacodyn. et de Therap.*, 1938, **58**, 221.

³ Macht, D. I., *J. Pharmacol. and Exp. Therap.*, 1923, **22**, 123.

⁴ Morrison, M., and Samwick, A. A., *J. A. M. A.*, 1940, **115**, 1708.

on successful intramedullar transfusion of human bone marrow and the brilliant experiments of Tocantins⁵ and O'Neill,⁶ who reported efficient absorption of blood, plasma, glucose, congo red and metallic mercury injected into the intramedullar canal of higher animals.

Ten experiments were made on dogs, 30 on cats, 75 on rabbits, 60 on guinea pigs, 20 on rats and 12 on mice. Many drugs and pharmacological agents have been studied and still others are being examined by injection into the intramedullar cavity, injections being generally made into tibia but sometimes into humerus and femur. In rabbits and smaller animals the bones are thin enough to admit of the puncture or boring of a stout needle, the caliber of which must conform to their size. In larger animals trocars of various sizes were used to make small apertures through the bone into the medullar cavity and through these openings metal canulae reached the marrow. Two groups of drugs were employed in this study, *i. e.*, (1) aqueous solutions of potent principles and (2) oils and other liquid drugs.

Aqueous Solutions. Well-known potent drugs soluble in water or physiological saline were injected into medullar cavities of various animals and their subsequent absorption was shown by characteristic systemic effects. As indicated by pharmacological responses elicited, all the drugs in the subjoined list were promptly absorbed through the bone marrow.

Morphine sulphate	Effect on respiration
Apomorphine	Emetic action
Cobra venom	Effect on circulation and respiration
Thebaine HCl	Convulsant action
Strychnine nitrate	Convulsions
Metrazol	"
Picrotoxin	"
Caffeine	Effect on circulation and respiration
Ouabain	Effect on heart
Sodium nitrite	Fall in blood pressure, methaemoglobin formation
Atropine sulphate	Mydriasis, paralysis of intestines
Pilocarpine HCl	Myosis, salivation, intestinal peristalsis
Physostigmin	Intestinal paralysis, twitching of skeletal muscle, slowing of heart
Nicotine	Typical picture of poisoning, death from paralysis of respiration
Epinephrine	Effect on blood pressure
Ephedrine	" " " "
Aconitine	Typical effect on respiration and circulation
Phenolsulphonphthalein	Excretion by kidneys
Insulin	Convulsions

⁵ Tocantins, L. M., PROC. SOC. EXP. BIOL. AND MED., 1940, 45, 292.

⁶ Tocantins, L. M., and O'Neill, J. F., PROC. SOC. EXP. BIOL. AND MED., 1940, 45, 782.

The following protocols illustrate some of the results obtained:

<p><i>Experiment of March 24, 1941</i> Rabbit weighing 2 kg Injected pilocarpine HCl, 2 mg to the cc, in tibia In 10 min. profuse salivation and mark- edly slowed heart-beat Myosis, active stimulation of intestinal peristalsis Gradual recovery</p>	<p><i>Experiment of April 4, 1941</i> Rabbit weighing 1.2 kg Injected 1 cc of phenolsulphonphthalein in tibia</p> <table border="0" style="margin-left: 20px;"> <tr> <td>Output first hour</td> <td style="text-align: right;">35%</td> </tr> <tr> <td> " second "</td> <td style="text-align: right;">50%</td> </tr> <tr> <td style="border-top: 1px solid black;">Total</td> <td style="text-align: right; border-top: 1px solid black;">85%</td> </tr> </table>	Output first hour	35%	" second "	50%	Total	85%
Output first hour	35%						
" second "	50%						
Total	85%						

Absorption of Oils and Other Liquid Drugs. The effects of various oils and "oily" solutions injected into the medullary cavity of bones were even more interesting. Thus evipal, introduced into the tibiae of guinea pigs, completely anesthetized them in a few minutes. So did avertin and chlor-butanol dissolved in olive oil. Pure benzyl benzoate, injected into tibia of a cat under paraldehyde anesthesia, was promptly absorbed as indicated by fall in blood pressure and depressed respiration.

Between the volatile or essential oils and the fixed oils there was a marked difference in rapidity of absorption. The volatile oils studied were oils of rose, rose geranium, rosemary, thyme, anise, orange, sassafras, cinnamon, cloves, tansy and wintergreen. Systemic effects from all these were usually noted a few minutes after their introduction into the bone marrow, *i. e.*, primary excitation, followed by depression, convulsions, coma and death, depending on dose injected.

Absorption of the so-called fixed or heavy oils through bone marrow usually proceeded more slowly. Thus chlor-butanol in olive oil, injected into tibiae of cats and guinea pigs, effected general anesthesia in from 5 to 10 minutes. Camphorated oil (N.F.) dissolved in linseed oil produced typical epileptic convulsions in 15 to 30 minutes. A-estradiol in olive oil, injected into tibiae of spayed rats, produced positive oestrus smears after a lapse of 3 days. Crystalline progesterone in sesame oil (Proluton) injected into Clauberg rabbits, effected typical progestational proliferation of the endometrium. Suspensions of heparin in olive oil or peanut oil exerted anticoagulant effects in rabbits for longer periods than intravenous injections of the aqueous solutions. Introduction of a few drops of croton oil into tibiae of guinea pigs and rabbits was followed in 15 to 30 minutes by powerful contractions of abdominal muscles, purgation, ejaculation in males, coma and death (intramuscular injections of this oil had little effect). Castor oil had no laxative effect, thus confirming the view generally held regarding its mechanism of action. Injections of Ruvertus⁷ oil, however, were mildly laxative. Doses of

⁷ Macht, D. I., and Barba-Gose, J., *J. Am. Pharm. Assn.*, 1931, **20**, 558.

0.2 cc of olive, mineral, peanut, peach kernel, sesame and cottonseed oils, respectively, exhibited no harmful effect in guinea pigs.

Absorption of Epinephrine. Introduction of *aqueous* solutions of epinephrine into medullar cavities of bones was promptly followed by a sharp rise in blood pressure with transient depression of respiration and a rapid return of the blood pressure in cats, dogs and rabbits to the normal or frequently below the normal level. This effect differed but little from the response elicited by intravenous injections of the drug in the same animals. When solutions of epinephrine *in oil* were used, however, a very different picture was obtained. Such a solution of epinephrine in peanut oil, injected into the *muscles* of cats, dogs and rabbits, effected no noticeable rise in blood pressure. When the oily solution was injected into a *medullar cavity*, however, a striking pharmacological picture was observed. Such intramedullar injections were followed by a prompt rise in blood pressure to a moderate height, not as marked as that following aqueous solutions of the drug but of long duration, lasting from 20 to 30 minutes (Fig. 1).

Summary. (1) The absorption of many drugs introduced into the bone marrow was studied in various animals. (2) Aqueous solutions of all such agents were rapidly absorbed as indicated by their characteristic systemic effects. (3) Intramedullar injections offer an especially useful means for pharmacological study of oils and oily solutions. (4) Volatile oils are rapidly absorbed through bone marrow but the fixed oils are absorbed more slowly, thus retarding absorption of active principles dissolved therein. (5) Epinephrine in oil, introduced into medullary canals, produces a marked and long-sustained rise in blood pressure, an effect which cannot be achieved by intramuscular injection of such an oil solution.

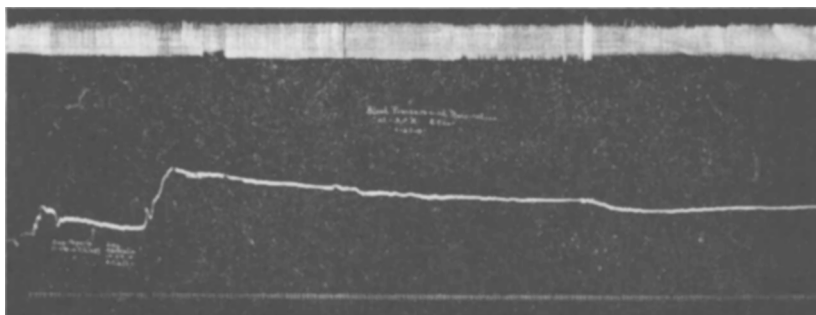


FIG. 1.
Effect of 2 mg of adrenalin in oil in tibia of cat.