

fasting level. Similar body weight curves were obtained with 22 other dose levels of the 3 samples of cottonseed pigment glands.

Summary. Acute toxicity studies were made on 3 different samples of cottonseed pigment glands administered orally to 228 rats in the form of slurries made with either distilled water or 2% ferrous sulfate solution. The LD50 values for the samples when administered in water were, respectively, 1140, 1490 and 2290 mg/kg. When given in 2% ferrous sulfate solution the samples were detoxified so that even such high doses as 7000 mg/kg for each were no longer toxic. There was little

effect on the body weight of all 99 rats which survived doses of ferrous sulfate-treated cottonseed pigment glands 3 to 6 times the LD50 value for water-suspended glands. Administration of pigment glands in 0.5% FeSO₄ did not detoxify them, and led to the death of all 24 rats given this preparation.

The author is indebted to Mr. H. F. Bialek for technical assistance, and to the Southern Regional Laboratory, U.S.D.A., New Orleans, La., for the samples of cottonseed pigment glands.

Received October 18, 1949. P.S.E.B.M., 1949, **72**.

Effect of 3-Ortho-toloxyl-1,2-propanediol (Tolserol, Myanesin) upon Electrogram of Human Cortex and Subcortex. (17463)

E. A. SPIEGEL AND H. T. WYCIS

From the Departments of Experimental Neurology and Neurosurgery, Temple University School of Medicine and Hospital, Philadelphia.

The sites of action of 3-ortho-toloxyl-1,2-propanediol (tolserol, myanesin) have not been exactly determined as yet, although there is suggestive evidence that this drug chiefly affects subcortical ganglia (Berger and Bradley;¹ Burke and Linegar;² Davison;³ Pugh and Enderby;⁴ Schlesinger *et al.*⁵). Particularly the experience that it is able to abolish petit mal discharges (Gammon and Churchill⁶) points to a thalamic effect, since these discharges seem to originate in thalamic nuclei (animal experiments of Jasper,⁷ human records of Wycis, Lee and Spiegel⁸).

A study of the effect upon the electrical

discharges of subcortical ganglia promised to supply more direct evidence. In the course of thalamotomy and mesencephalotomy operations carried out by means of our stereoencephalotome (Spiegel and Wycis⁹), we had an opportunity to record the potentials of human diencephalic and mesencephalic structures preceding the production of the lesions.

The effect of tolserol upon the electroencephalogram (scalp electrodes in the frontal and in the occipital region), upon the electrical discharges of thalamic nuclei (dorso-medial nucleus; lateral nucleus), of the hypothalamus, and of the tectum of the midbrain was studied. Needle electrodes consisting of an inner stylet, insulated except for the tip, and an outer sheath insulated except for a ring 3.0 mm above the tip of the stylet were inserted by means of the stereoencephalotome. Monopolar as well as bipolar leads were used. For monopolar recording, the tip of the inner

¹ Berger, F. M., and Bradley, W., *Brit. J. Pharm.*, 1946, **1**, 265.

² Burke, J. C., and Linegar, C. R., *Fed. Proc.*, 1948, **7**, 208.

³ Davison, W. H. A., *Brit. Med. J.*, 1948, **1**, 544.

⁴ Pugh, J. I., and Enderby, G. E. H., *Lancet*, 1947, **2**, 387.

⁵ Schlesinger, E. B., Drew, A. L., and Wood, B., *Am. J. Med.*, 1948, **4**, 365.

⁶ Gammon, G. D., and Churchill, J. A., *Am. J. Med. Sc.*, 1949, **217**, 143.

⁷ Jasper, H. H., and Droogleever-Fortuyn, J., *Res. Publ. Assn. Nerv. Ment. Dis.*, 1947, **26**, 272.

⁸ Wycis, H. T., Lee, A. J., and Spiegel, E. A., *Conf. Neur.*, 1949, **9**, 264.

⁹ Spiegel, E. A., Wycis, H. T., Freed, H., and Lee, A. J., *Proc. Soc. Exp. Biol. and Med.*, 1948, **69**, 175.

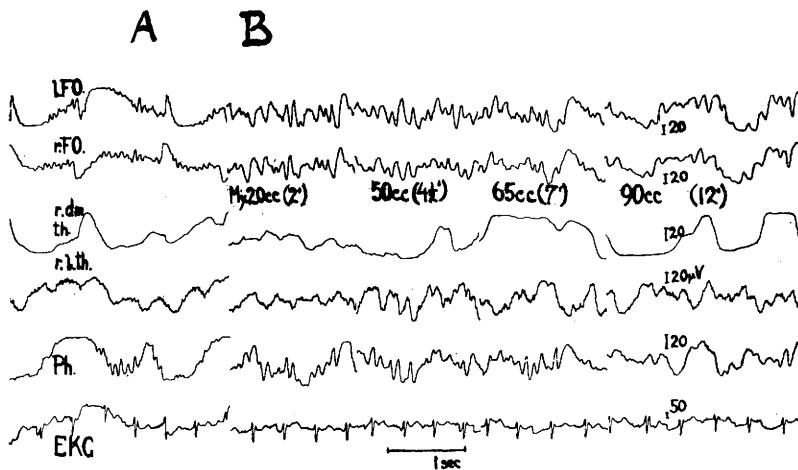


FIG. 1.

Effect of intravenous injection of 2% Tolserol solution in a schizophrenic patient chiefly upon the EEG (LFO bipolar record from left frontal and occipital scalp electrodes, rFO bipolar record from right frontal and occipital scalp electrodes). No definite effect upon the dorsomedial nucleus (r. dm. th) and the lateral nucleus (r l th) of the right thalamus. No definite changes in the pharyngogram (Ph) and the electrocardiogram (EKG). A large part of the right dorsomedial nucleus is degenerated by a previous thalamotomy. A before, B after injection of Tolserol (Myanesin My). Time after injection is indicated in brackets. Anesthesia: .6 mg Atropine sulf.; 30 cc Paraldehyde; Demerol 37.5 mg; 0.5 g Sod. Pentothal; N_2O-O_2 (3:1).

stylet served as the active, the lobe of the homolateral ear as the "indifferent" electrode. For bipolar recording the tip of the stylet served as the one and the bare ring on the sheath as the 2nd electrode. Simultaneously the electrocardiogram and the electrical discharges lead off from the roof of the pharynx were recorded. These records were obtained in schizophrenic patients, cases of depression and obsessive compulsive neuroses preceding thalamotomy and in cases of unbearable pain preceding mesencephalotomy. All patients were under nembutal or pentothal, N_2O-O_2 anaesthesia; 50-100 cc 2% Tolserol* were injected intravenously.

The following changes of the electrical activity were observed: In some instances, the fast, low voltage oscillations of the EEG of the anesthetized patients were replaced by slower waves of higher amplitude (Fig. 1). The speed of the injection seems of importance, if one wishes to demonstrate alterations of the EEG. We observed the above described effect, if the first 50 cc of the drug were

injected within 4-5 minutes and the following 50 cc within 6-8 minutes. In contrast to the susceptibility of the cerebral cortex to tolserol, we failed to obtain definite changes of the EEG following the injection of curare in doses sufficient to produce peripheral paralysis. This latter observation is in agreement with the findings of Harvey,¹⁰ Everett,¹¹ and Girden.¹² While no definite changes in the discharges of the dorsomedial nuclei (dm th) and of the lateral nuclei (lat th) of the thalamus were found (Fig. 1), the hypothalamic lead (Hm and Hb) showed a definite depression of the discharges interrupted by the appearance of burst of slow waves of high amplitude (Fig. 2). These changes appeared at a stage when a cortical effect was not definite as yet. The same applies to the tectum of the midbrain whose fast, low voltage discharges were replaced by high 3-5/second waves (Fig. 3).

Summary: Tolserol has a definite effect

¹⁰ Harvey, A. M., *Fed. Proc.*, 1948, **7**, 458.

¹¹ Everett, G. M., *J. Pharm. and Exp. Therap.*, 1948, **92**, 246.

¹² Girden, E., *J. Neurophysiol.*, 1948, **11**, 169.

* Kindly supplied by Dr. H. Sidney Newcomer, E. R. Squibb and Sons.

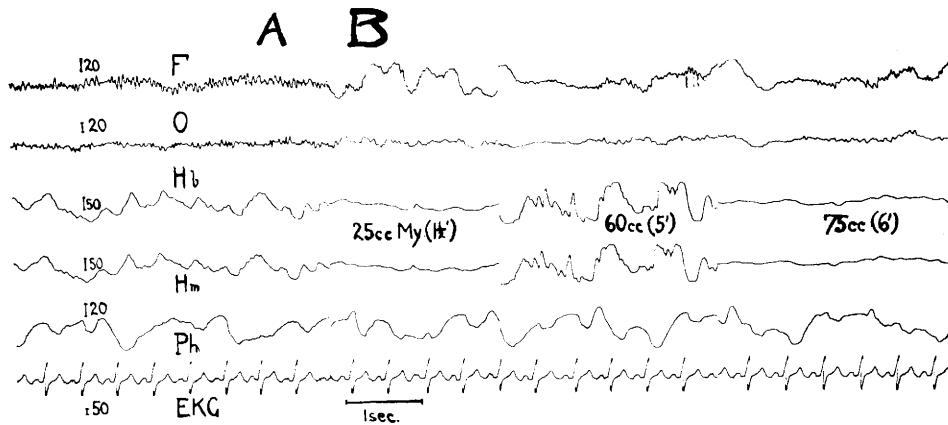


FIG. 2.

Effect of intravenous injection of 2% Tolserol solution (My) chiefly upon the hypothalamogram in a paranoid schizophrenic. Hb bipolar, Hm monopolar records from the hypothalamus. Note that the pharyngogram does not reflect the changes in the hypothalamogram. F bipolar record from the frontal areas, O from the occipital areas (scalp electrodes) A before, B after injection of the drug. Anesthesia: Atropine sulf. 0.4 mg; Sod. Phenobarbital 0.2 g; Sod. Pentothal 1.3 g; Curare 100 units; N_2O-O_2 .

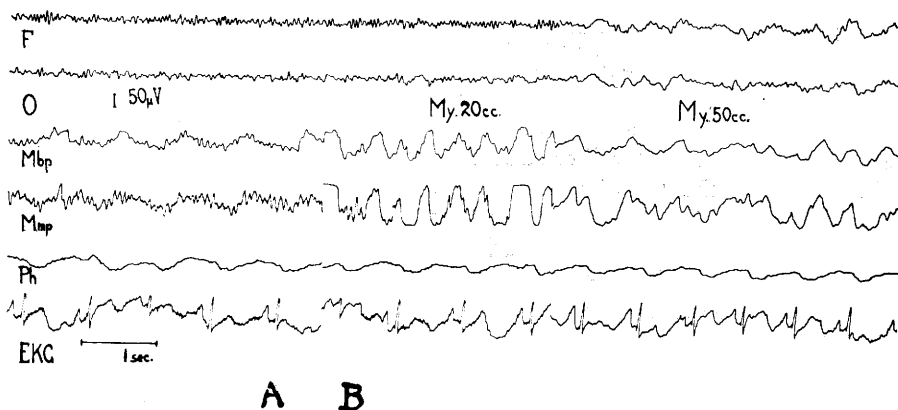


FIG. 3.

Effect of intravenous injection of 2% Tolserol solution (My) upon the tectum mesencephali in a case of severe pain. Mbp bipolar, Mmp monopolar records from the tectum of the midbrain. F bipolar frontal, O bipolar occipital records (scalp electrodes). A before, B after injection of the drug. Anesthesia: Atropine sulf. 0.6 mg; Nembutal 200 mg; Curare 100 units; Sod. Pentothal 0.375 g; N_2O-O_2 .

upon the electrical discharges of the human cerebrum; the most pronounced changes were found in the electrical activity of the hypothalamus and of the midbrain.

We wish to express our appreciation to Dr. L. Krumperman and Dr. B. Siman from the Anesthesia Department for their kind cooperation.

Received October 14, 1949. P.S.E.B.M., 1949, 72.