

monary ventilation. Whether the calculations on the acid base equilibrium of resting tissue can be applied to the respiratory center whose activity and metabolism are augmented by oxygen lack remains to be determined by other methods. Until such crucial experiments are performed, however, our present results might be interpreted as indicating a direct stimulating action of oxygen lack independent of increased hydrogen ion concentration.

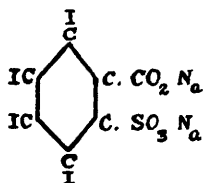
5004

A Pharmacological Study of Sodium Tetra-iodo-ortho-sulpho Benzoate.

DAVID I. MACHT AND DANIEL TWISS.

From the Chemical and Pharmacological Research Laboratories, Hynson, Westcott & Dunning, Baltimore.

This substance was synthesized by one of the authors and studied pharmacologically in an intensive and extensive way by the other in connection with a research instituted at the suggestion of an orthopedic surgeon, Dr. Henry Keller, of New York, in quest of a drug suitable for injection into joint cavities for facilitation of x-ray examinations. The compound is a di-sodium salt of tetra-iodo-ortho-sulpho benzoic acid having the following structural formula:



It is a beautiful light yellow crystalline powder freely soluble in water, being practically odorless and tasteless. The molecular weight of this compound is 789.68 and its iodine content, 67.72%. An isotonic solution of the salt requires a concentration of 11.3%, whereas comparative studies on sodium iodide were found to produce isotonic solutions in the concentration of 2.2%. Such an isotonic solution of the new compound contains about 4 times as much iodine as an isotonic solution of sodium iodide and, in addition, is devoid of the objectionable pharmacological features of an inorganic salt solution.

A 10% solution of the salt was made the starting point for all the experiments performed. Such solutions were found to be non-irritating on instillation into the conjunctival sac and application to other mucous membranes. Subcutaneous and intramuscular injections into rabbits, dogs and other animals gave no evidence of local irritation or infiltrations. Intravenous injections of the solution were well tolerated by all higher animals and quantities of 100 mg. per kilo produced no appreciably toxic effect in intact animals. The lethal dose on intravenous injection for rabbits was found to be 0.5 gm. per kilo, for cats under ether anesthesia, 0.5 gm. per kilo, and for dogs under ether anesthesia, 0.4 gm. per kilo. Blood pressure and respiratory tracings studied on the cat and dog showed that after doses of from 100 to 300 mg. per kilo, there was practically no effect on the respiration or the circulation. The lethal doses produced a primary fall in blood pressure which was followed later by paralysis of the respiratory center and last of all by arrest of the heart. The yellow compound, when injected intravenously, is excreted rapidly and almost entirely by the kidneys, only a trace of the compound being found in the bile. On administration of solution by the stomach tube, the compound is also excreted by the kidneys and not at all by the liver. In testing for the presence of the tetra-iodo-ortho-sulpho benzoate in urine and other secretions, the firmly bound iodine cannot be detected by the simple method of using sodium nitrite and shaking out with chloroform, but its presence can be easily demonstrated by first disintegrating the compound by heating almost to dryness, then taking up the residue in water, and testing by the usual chemical methods. Studies on kidney function after intravenous injections of large doses of the compound revealed that it produced no renal irritation.

Studies on isolated tissues showed that the new compound was not depressant for smooth muscle in solutions of 1:1,000. In this connection, moreover, it was noted that it possessed peculiar sensitizing properties for the true sympathetic nerve terminals in that subsequent treatment with epinephrine of such tissues as vas deferens, ureters and uterus gave a potentiated contraction of the muscle as compared with normal controls which were not previously treated with the drug. In view of the benzoate radicle, experiments were made on rabbits to ascertain whether the compound possessed antipyretic properties. No antipyretic effect was noted in animals with artificial fever and, indeed, in normal rabbits a slightly pyretic effect, or an increase in temperature, was produced after intravenous injection of the drug.

Psychopharmacological experiments on albino rats, trained in the circular maze according to the methods of Macht and his collaborators,¹ proved that the compound produced no depression either of the central nervous system or of the neuromuscular mechanism. Phytopharmacological studies, carried out on seedlings of *Lupinus albus*, according to the methods of the senior author,² showed that the compound was quite toxic for plant protoplasm although it was little toxic for isolated animal tissues. This was a striking confirmation of the original findings of Macht and Livingston concerning the extreme sensitiveness of plant protoplasm to benzoates.³

In view of the pharmacological findings given above and the relatively low toxicity of the drug, clinical observations were justified and were made on selected cases by Dr. Keller in the orthopedic clinic, the results of which are published elsewhere.⁴ Dr. Keller found that from 25 to 30 cc. of a 10% solution could be easily injected into the knee joint and gave remarkably well defined roentgenographs revealing structures and conditions around joints which could not be detected by ordinary x-ray examination without previous injections of the drug. Because of the rapid and almost complete secretion of the drug through the urinary system, carefully conducted investigations on selected urological cases are in progress under the supervision of competent genito-urinary specialists. A full description of the chemical and pharmacological studies will be published by the authors later.

5005

Experimental Studies on Visualization of Joints by Injections of a Drug.

HENRY KELLER. (Introduced by David I. Macht.)

From the Orthopedic Department of the Neurological Hospital, New York City.

By the term arthritis the clinician usually means an inflammatory reaction involving the region of a joint. Such an inflammation may involve the synovial membrane alone, when it is termed more strictly synovitis. Usually, however, the inflammatory process involves the

¹ Macht and Mora, *J. Pharmacol. and Exp. Therap.*, 1920, xvi, 219.

² Macht and Lubin, *J. Pharmacol. and Exp. Therap.*, 1924, xxii, 413.

³ Macht and Livingston, *J. Gen. Physiol.*, 1922, iv, 573.

⁴ Keller, *Proc. Soc. Exp. Biol. and Med.*, 1930, xxvii, 852.