# Some Effects of Paracolon Bacteremia.* (18613)

RUSSELL M. NELSON† AND CLARENCE DENNIS.

*From the Department of Surgery, School of the Medical Sciences, University of Minnesota.*

We and our associates described the loss of many dogs from poorly understood causes after total body perfusions with a combined pump-oxygenator apparatus(1). Many of these dogs died of a hemorrhagic complication leading to profuse gastro-intestinal hemorrhage. We previously described the production of a hemorrhagic state by the canine infusion of hemolyzed whole blood(2). This condition was characterized by gastro-intestinal hemorrhage, serous cavity effusions, disseminated petechiae, prolongation of blood coagulation time, and death. It was determined that plasma hemoglobin was not the offending agent and that other etiological factors must be operating(2).

Subsequently, it has been learned that the blood used in these and other experiments was heavily contaminated with bacteria, with a Gram-negative micro-organism, the Paracolon bacillus predominating. Colony counts were, of course, much higher in blood which had been removed from the refrigerator for several hours, as was the case with the blood that had been hemolyzed. The control, non-hemolyzed blood, which had been refrigerated almost constantly, had very little bacterial growth. With this information, then, it was decided to ascertain the effects of intravenous canine infusion of these bacteria alone, uncomplicated by the variables of simultaneous blood administration.

*Methods.* Dogs of 23 kg average weight were anesthetized with sterile solutions of pentobarbital given intravenously. With strict aseptic technic throughout, a small inguinal incision was made in order to facilitate the obtaining of arterial blood samples. An 18-gauge needle was inserted into the vein of the foreleg, to which was connected the intravenous infusion flask. A 14 hour culture of the paracolon bacillus *(Paracolobactrum intermedium)* was centrifuged, the supernatant broth discarded, and the small residue in the bottom of the culture tubes resuspended in 50 cc of sterile saline solution. This suspension was infused intravenously into 9 dogs. The average time for infusion was 10 minutes. Four other dogs served as controls, receiving only sterile infusion of the same volume, in addition to the prolonged anesthesia (about 6 hours).

*Results.* All 9 experimental dogs died. All but 2 died within 14 hours, with the shortest period of survival being 2½ hours. Prior to death, there were retching, salivation, hyperventilation, muscular weakness, frequent loose stools, which were often bloody, and coma. No such ill effects were recognized in the control dogs. All but one of the experimental dogs showed an increase in coagulation time, and all but 2 showed gross gastro-intestinal hemorrhage.

Blood cultures were taken at 4 periods: 1. pre-infusion, 2. immediately after infusion, and the others at 3 and 5 hours. All the control and pre-infusion cultures were sterile. The culture drawn immediately after the bacterial infusion exhibited extremely heavy growth. The 3 hour culture still contained a heavy growth, but at 5 hours, the bacterial count had diminished considerably, indicating that the bacteria were being removed from the circulating blood stream.

*Comment.* Several reports have appeared in the literature of experiments dealing with metabolic aspects of shock, and perfusions with artificial heart, lungs and kidneys performed without bacteriologic proof of asepsis.

* Supported by a research grant from the U.S.P.H.S. and a grant from the Graduate School of the University of Minnesota.

† Formerly Research Fellow, U.S.P.H.S., now U.S. Army Reserve Corps, Army Medical Service Graduate School, Washington, D. C.

1. Dennis, C., Karlson, K. E., Eder, W. P., Nelson, R. M., Eddy, F. D., and Sanderson, D., *Surg.*, 1951, in press.

2. Nelson, R. M., Eder, W. P., Eddy, F. D., Karlson, K. E., and Dennis, C., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 208.

For instance, Frank, Seligman, and Fine(3) described a similar syndrome in dogs which had been subjected to exsanguination to shock levels, and then reinfused with blood, which had been collected in non-sterile containers, in an effort to evaluate the stage of irreversibility of shock. The similarity of this syndrome to that seen on occasion in human patients is striking(4).

Waisbren has found that patients with advanced cirrhosis not infrequently develop a hemorrhagic syndrome in association with Gram-negative spore-former bacteremia(5).

Aub and his associates reported that many of the effects of trauma to muscle in the dog are attributable to contaminating Clostridia and concluded with a plea for care in eliminating sepsis in muscle trauma experiments(6). Our present report extends the scope of the importance of asepsis and calls attention to the lethal effect of organisms previously considered non-pathogens.

*Conclusion.* Dogs receiving an intravenous infusion of a 14 hour culture of the Paracolon Bacillus exhibited profound illness and rapid death. Canine experiments in which conclusions are to be based on survival in apparent health for more than 2 or 3 hours should be conducted with precise aseptic technic rather than general cleanliness alone, in order to eliminate the influences of bacterial contamination.

The authors express thanks to Dr. J. T. Syverton for kindly counsel and aid in the prosecution of this study.

3. Frank, H. A., Seligman, A. M., and Fine, J., *J. Clin. Invest.*, 1945, v24, 435.

4. Friesen, S. R., and Nelson, R. M., *Southern Surgeon*, 1951, in press.

5. Waisbren, Burton A., personal communication.

6. Aub, J. C., Brues, A. M., Dubos, R., Kety, S. S., Nathanson, I. T., Pope, A., and Zamecnik, P. C., *War Med.*, 1944, v5, 71.

Received February 28, 1951. P.S.E.B.M., 1951, v76.

## Central Nervous System Activity of Some 2-Pyridyl Compounds.* (18614)

J. F. O'LEARY, D. E. LEARY, AND I. H. SLATER. (Introduced by H. C. Hodge)

*From the Divisions of Orthopaedic Surgery, of Surgery, of Pharmacology and Toxicology, of Radiation Biology, of the University of Rochester School of Medicine and Dentistry.*

In studies employing our previously described technics used in screening drugs for anti-convulsant activity(1), a variety of chemical structures containing a 2-substituted pyridine grouping have been investigated (Table I). Several piperidine and quinoline compounds of similar configuration have been examined for comparative purposes. The syntheses of a large majority of these compounds have been described recently by Boekelheide and Agnello(2).† The pharmacological actions of previously studied pyridine derivatives have been reviewed by Von Oettinger(3). More recently Fromherz and Spiegelberg(4,5) have investigated a series of 3-substituted pyridine compounds from a pharmacodynamic viewpoint, and Valenzuela and Huidobro(6) have studied the effects of some similar compounds upon neuromuscular transmission. No studies of the presently considered 2-substituted pyridine compounds re-

* Aided by a grant from the National Foundation for Infantile Paralysis.

1. Slater, I. H., O'Leary, J. F., Leary, D. E., *J. Pharmacol.*, 1950, v100, 316.

2. Boekelheide, V. and Agnello, A. J., *J. Am. Chem. Soc.*, 1950, v72, 5005.

† These investigators have kindly supplied us with these compounds.

3. Von Oettingen, W. F., *The Therapeutic Agents of the Pyrrole and Pyridine Groups*, Edwards Brothers, Inc., Publishers, Ann Arbor, Mich., 1936.

4. Fromherz, K., *Schweiz. Med. Wochensch.*, 1949, v79, 521.

5. Fromherz, K., Spiegelberg, H., *Helv. Physiol. Acta*, 1948, v6, 42.

6. Valenzuela, F., and Huidobro, F., *J. Pharmacol.*, 1948, v92, 1.