A Simple Method for Production of DCA Hypertension in Rats. (18909)

S. Charles Freed, Meyer Friedman, and Ray H. Rosenman.*
From the Harold Brunn Institute, Mount Zion Hospital, San Francisco, California

The chronic administration of desoxycorticosterone salts, in particular desoxycorticosterone acetate (DCA), has been employed to produce hypertension in various laboratory animals(1). It is generally agreed, however, that DCA hypertension uniformly occurs only when certain favorable conditions are present(2). In the rat these include a large dosage of DCA, a young animal, an adequate amount of available sodium, and the removal of one kidney, to "sensitize" the animal to the effects of DCA(3). Despite the presence of these suitable conditions, however, certain investigators have been unable to produce DCA hypertension of satisfactory degree or with any measure of regularity in the rat(2) or in the dog(4). We encountered similar difficulties and have attempted to introduce various modifications which might produce more regularly and frequently in our rats, significant hypertension, without marked general toxicity. The most successful method devised by us has been the following.

A one-stage operation is performed through bilateral dorsal incisions in rats of the desired age. This consists of a uninephrectomy with the application of a figure-of-eight silk ligature about the poles of the remaining kidney (Grollman)(5). When such rats are fed a stock ration, with tap water to drink, hypertension develops in from 30 to 60% of our operated animals. In an extensive experience with this technic, we have found that a systolic pressure exceeding 135 mm of Hg develops in less than 5% of rats if this level has not been reached and maintained during a 4-week postoperative period. Ordinarily, the varying number of rats in which hypertension fails to develop or to persist are discarded. In 3 independent groups of such rats we have observed that the administration of DCA in the absence of increased sodium intake in the drinking fluid, regularly has produced a significant hypertension without gross general toxicity.

A representative series of rats will illustrate this method. A group of 7-week-old male rats (Long-Evans strain) was subjected to the Grollman procedure(5). The systolic blood pressure was obtained at weekly intervals by the microphonic method of Friedman and Freed(6). During the ensuing 10-week observation period, 10 of those rats (Group I) which failed to develop persistent hypertension were maintained on the stock ration with tap water to drink. They remained normotensive, gained weight normally, and did not manifest any untoward effects or evidence of renal insufficiency. The average blood pressure at the end of this 10-week period was 119 mm of Hg. (Range: 110 to 135). These 17-week-old rats were then given 4 mg of DCA in benzyl alcohol†, subcutaneously, 3 times weekly. A group of 8 intact, 13-week-old animals (Group II) was also injected with the same dosage of DCA and received 0.9% sodium chloride in the drinking fluid. Another group of 11 seven-week-old rats (Group III) was uninephrectomized and given 0.9% saline to drink at the same time that DCA was administered in the same dosage.

From Fig. 1 it can be seen that the average blood pressure of the rats with the "renal tie" (Group I) rose progressively and stabilized at significantly hypertensive levels

* Research Fellow of the American Heart Association.

1. Selye, H., *Stress, Acta,* Montreal, 1951.
2. Sayers, G., *Physiol. Rev.,* 1950, v30, 241.
3. Corcoran, A. C. In Pituitary-Adrenal Function, A Symposium. Horn-Shafer Co., Baltimore, 1951.
4. Summers, J. E., *Am. J. Physiol.,* 1948, v154, 119.
5. Grollman, A., Proc. Soc. Exp. Biol. and Med., 1944, v57, 102.
6. Friedman, M., and Freed, S. C., Proc. Soc. Exp. Biol. and Med., 1949, v70, 670.

† We are grateful to Dr. Abbott W. Allen of the Schering Corporation for generous supplies of DCA employed in these studies.

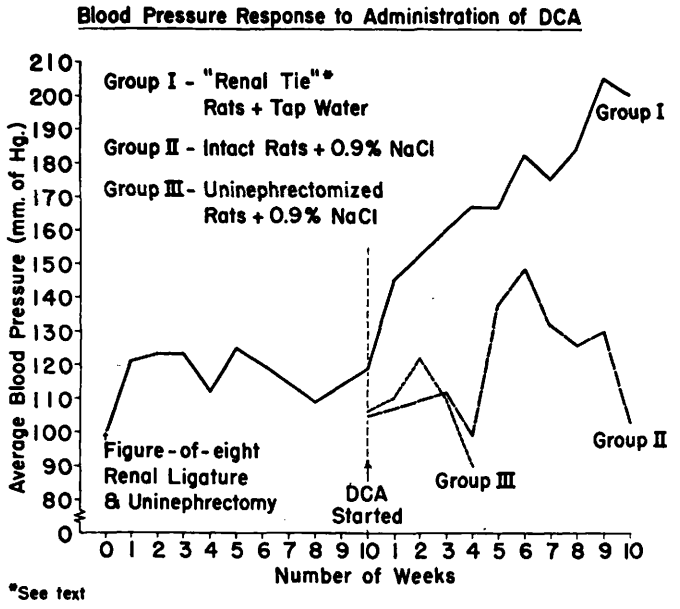

FIG. 1.

during the ensuing 11-week interval, well above the levels of the control animals. Thus, the average blood pressure of the experimental rats was 195 mm of Hg (Range: 156 to 230) at the eleventh week. Growth and weight gain were not disturbed and the general condition of these hypertensive rats remained good, with no outward evidence of toxicity. Only one rat died during the experimental period, at the ninth week, the cause of death unknown.

The average blood pressure of the intact rats receiving DCA and drinking 0.9% saline (Group II) rose from 105 mm of Hg (Range: 92 to 110) to 149 mm of Hg (Range: 120 to 180) at the sixth week. However, this response was not maintained and the average blood pressure of these rats had decreased by the tenth week to 103 mm of Hg (Range: 66 to 159). The average blood pressure of the uninephrectomized rats drinking 0.9% saline (Group III) failed to rise to hypertensive levels during the administration of DCA. Progressive loss of weight and other evidence of toxicity were observed in both groups of animals. This was so marked in the rats of Group III that the experiment was terminated.

Summary. The administration of DCA to normotensive rats following a figure-of-eight "renal tie" and uninephrectomy has been found to induce consistently a marked hypertension. Similar treatment of both intact and uninephrectomized rats drinking physiologic saline was ineffective in this respect. Hypertension was readily induced in the "renal tie" animals despite the absence of excess sodium chloride and their older age.

Received July 15, 1951. P.S.E.B.M., 1951, v77.