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Device to Control Constriction of Main Renal Artery for Production of Hypertension in Small Animals.* (25058)

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Various methods have been employed for production of experimental renal hypertension in the rat, but most of them have drawbacks. For small animals, the production and application of the original silver clamp devised for constriction of the main renal artery in the dog and other large animals(1) are impractical. The simplest method is the constriction of the main renal artery by a silver clip, or band(2-4). This method lacks adequate means of controlling degree of constriction of the artery. To this end, an instrument has been constructed with which this constriction can be made uniform and which facilitates production of acute and chronic hypertension in a high percentage of rats of equal weight. The instrument was fashioned from old type surgical needle holder. Through one jaw of instrument (Fig. 1, A) a screw (B) is inserted, the end of which comes in contact with inner surface of opposite jaw (C). Adjustment of this screw keeps the jaws apart to any desired extent, and turning of screw in one or the other direction controls the space left between the jaws, the width of which can be definitely determined. This is done by closing the jaws of forceps on blades of a mechanic's feeler gauge, graduated in fractions of an inch, in such a way that, when the screw touches the opposite jaw, the desired gauge blade can be slipped snugly into the space. By testing the effect of the forceps on a gauge blade of next size, larger and smaller, a check on correct adjustment can be made. The jaws of the instrument must be rigid toward the tip, and the surfaces which oppose one another must be machined perfectly flat and smooth. The silver clip (Fig. 1, D & E) for constriction of main renal artery is made from a strip of annealed, rolled, silver ribbon 2 mm wide and 0.127 mm thick. This strip is divided into sections measuring 6 mm in length, and the edges are filed round and smooth. The clip is then bent into a U-shape, over an ordinary pin, and the 2 ends are bent slightly outward (Fig. 1, E), to facilitate application.

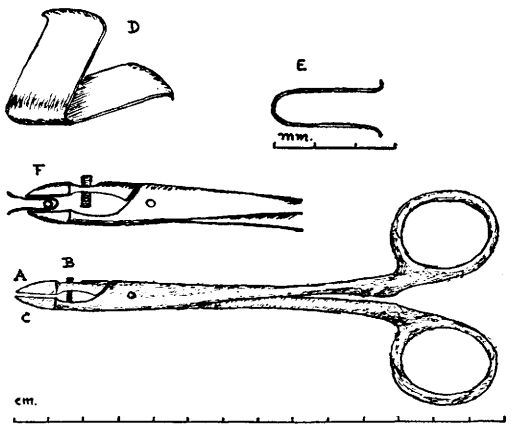

FIG. 1.

Application of clip. Through a costo-lumbar incision, with kidney retracted toward the abdomen, the renal pedicle is exposed, the artery is dissected clean, and the clip is slipped around it, near the aorta. The free edges of the clip are then approximated by means of a hemostat, to enclose the artery. With the jaws of instrument previously adjusted to desired gauge, about half of the "U" of the clip, including the rounded end, in which the ar-

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tery rests (Fig. 1, F), is grasped in the jaws of the forceps and compressed firmly so as to constrict the vessel to the desired degree.

It has been found by experience that for female rats, weighing about 150 g, constriction of only one main renal artery, with the forceps set to leave a space of 0.014″ (or 0.355 mm) leads to development of hypertension in the majority of animals. The wall of the renal artery is actually compressed by this procedure to outside thickness of about 0.1 mm. Greater constriction, which leads to complete necrosis of the kidney, or inadequate constriction, is ineffective in raising the blood pressure. For female rats weighing around 200 g, a free space of 0.015″ is necessary, and for those weighing around 250 g, a free space of 0.016″ is most satisfactory. In the case of rapidly growing young male rats, a degree of constriction, adequate for a young female rat of equal weight may prove to be too tight and eventually lead to necrosis of the kidney, as the animal grows. This must be taken into consideration.

Summary. An instrument has been described which permits accurate control of degree of constriction of the main renal artery in small animals and facilitates production of hypertension in a large percentage of such animals.

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Metrotropic Activity of Some 21-Haloprogesterone Derivatives.* (25059)

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Recent interest in obtaining orally active progestational agents resulted in synthesis of many structural modifications of progesterone and 19-nortestosterone. Certain of these materials have been shown to be of value clinically. In the progesterone series, metrotropic activity has been reported for a series of 9-α and 12-α-halogenated derivatives of progesterone(1). 9α-Bromo-11-oxoprogesterone was effective clinically upon oral administration; its potency was rated as equal to that of 17α-hydroxyprogesterone acetate and about 2 to 3 times more potent than ethisterone(2,3). 9α-Fluoro-11β-hydroxyprogesterone and its 17α-hydroxy analogue were weak metrotropic agents in rabbits(4). These same agents were reported to be more active than progesterone as antagonists of estrone-induced uterine growth in rats(5). In a similar test 9α-fluoro-11β-hydroxy and 9α-fluoro-11-oxoprogesterone were about equal to progesterone(1). The present communication deals with progesterone-like activities and structure-function relationships of several 21-halogenated steroids.

Materials and methods. The following steroids were used: Progesterone, 21-fluoroprogesterone, 21-chloroprogesterone, 17α-hydroxyprogesterone, 17α-hydroxy-21-fluoroprogesterone, 17α-hydroxy-21-chloroprogesterone, 17α-acetoxyprogesterone, 17α-acetoxy-21-fluoroprogesterone, 17α-acetoxy-21-chloroprogesterone, 17α-acetoxy-21-bromoprogesterone, 17α-acetoxy-21-iodoprogesterone, 6α-methyl-17-acetoxy-progesterone, 6α-methyl-17-acetoxy-21-fluoroprogesterone and 6α-methyl-17-acetoxy-21-chloroprogesterone. Estimates of activity were obtained using the Clauberg assay, uterine carbonic anhydrase assay and the intra-uterine (McGinty) assay. *Clauberg Assay*(6). The test compound was administered subcutaneously or orally over 5 days to immature female rabbits previously primed for 6 days with 5 μg estradiol-17β. On day following last treatment, animals were sacrificed and

* The new steroids described in this study were prepared by Drs. C. G. Bergstrom, P. B. Sollman and R. M. Dodson, Division of Chemical Research, G. D. Searle & Co.