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Effect of Thiazide Drugs on Renovascular Hypertension in Contrast to Their Effect on Essential Hypertension.* (28868)

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Drugs of the benzothiadiazine family have proven extremely useful over the past 5 years for lowering arterial pressure of patients with benign essential hypertension. At least 50% of patients with mild or moderate essential hypertension will get a substantial reduction in blood pressure with the use of the thiazide drugs alone. Even severe essential hypertension is commonly improved by thiazide drugs. Furthermore, thiazide drugs also have the property of potentiating the action of various other types of anti-hypertensive drugs. In a previous study we could find no change in the electrolyte composition of arteriolar walls under the influence of thiazide drugs (1). However, the secretory activity of the granular juxtaglomerular cells appeared to be enhanced by the drug(1), and Winer has shown that a renin-like substance appears in increased concentration in the plasma of human beings taking thiazides(2). Such findings are reminiscent of the effects of a low intake of sodium, and it seems quite likely that the thiazides lower the blood pressure of patients with essential hypertension through the same mechanisms that act in conjunction with a drastic reduction of dietary sodium (3).

We had noted previously that an extreme reduction in sodium intake was quite ineffective in preventing or alleviating the hypertension produced in rats by narrowing one renal artery ("renovascular" hypertension) (4). We reasoned that if the thiazide drugs reacted on various forms of hypertensive disease in the same manner as did a drastic restriction of dietary sodium, then these drugs should be similarly ineffective in "curing" renal hypertension in the rat. The validity of this supposition was tested in the following experiment.

Methods. 20 male rats of the Wistar strain had become hypertensive 4 months after one renal artery had been narrowed, the contralateral kidney remaining intact. The arterial pressure of each rat was at least 160 mm Hg at this time, as measured with the microphonic method(5). The normal arterial pressure of rats of this age and strain averages 132 mm Hg (SD $\pm$ 9 mm Hg). Thus the blood pressure of our experimental rats was distinctly in the hypertensive range. During a 3-week preliminary period, the blood pressure of each rat was determined twice weekly for a total of 6 determinations. At this point, we began dissolving the thiazide drug, methyclothiazide, in the rats' drinking water, adding 86.4 mg of the drug per liter of tap water. In preliminary experiments it was determined that this dosage level produced a near maximum thiazide effect. The rats continued to ingest the thiazide drug in their drinking water for a period of 5 weeks. Then they were taken off the drug and switched back to ordinary tap water for a 4-week follow-up period. During the entire experiment, blood pressure and body weight of each rat were determined twice weekly.

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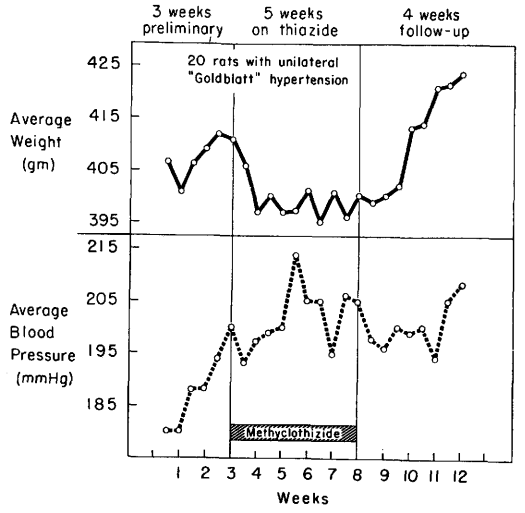

FIG. 1. Average arterial pressure and body weight of group of hypertensive rats receiving methyclothiazide.

The data were averaged for the group of 20 rats. These average values are depicted in Fig. 1.

Results. The average arterial pressure of the hypertensive rats was 188 mm Hg during the 3-week preliminary period. Moreover, the average blood pressure rose slightly during this 3-week period, blood pressure at the end of the preliminary period averaging 200 mm Hg. During the 5 weeks when the rats were ingesting methyclothiazide, the average blood pressure of the group actually rose slightly to a mean of 205 mm Hg at the end of the 5-week period. After discontinuing the drug, the blood pressure remained at about the same level during the 4-week follow-up period, averaging 207 mm Hg at the end of the 4 weeks.

The average weight of the rats was 411 g at the end of the 3-week preliminary period. During the first week on methyclothiazide, each rat lost an average of about 13 g of weight. During the latter 4 weeks on methyclothiazide, their weight averaged 398 g per rat. Their weight was quite stable during these latter 4 weeks, suggesting that weight loss was not due to poor appetite. In confirmation of this, the rats all appeared quite healthy during the weeks on methyclothiazide. The decrease in weight from 411 g to 398 g represents a 3.2% weight loss. Four weeks after discontinuing methyclothiazide, the weight of the rats had increased an average of 6.3%, from 398 g to 423 g.

Discussion. When the rats started ingesting methyclothiazide, they lost about 3% of their body weight within a week, then leveled off during the succeeding 4 weeks. This is quite reminiscent of patients who commonly lose 2 kg of weight after large doses of thiazides(6,7). Moreover, our group of rats regained their weight when the drug was discontinued, just as patients do. This weight loss during thiazide administration would indicate that the rats were getting enough drug to be distinctly under its influence. Nevertheless, the drug was completely ineffective in lowering the blood pressure of these hypertensive rats. Its action in renal hypertension was thus similar to that of a low intake of sodium. The experimental results would also indicate that in the rat at least, large doses of thiazide have no direct dilating effect on arterioles, an action which has been debated in regard to human beings.

Narrowing the renal artery of a lone kidney in almost any terrestrial mammal will produce hypertension. It would be extremely unlikely that the mechanism of this type of hypertension is different in the various mammalian species. Thus, the hypertension produced by narrowing the renal artery in a rat probably operates through the same chain of causation as the hypertension produced by a narrowed renal artery in man. For this reason, it may prove clinically useful to give selected hypertensive patients a trial of large doses of thiazide drugs alone. If the blood pressure becomes considerably lowered while on the drug, the patient would be more likely to have essential hypertension than renovascular hypertension. This thesis is gradually being tested in our hypertension clinic.

It has often been pointed out that the physiological derangement in renovascular hypertension is closely similar to that of essential hypertension(8). However, renovascular hypertension in the rat does not respond to thiazide drugs or sodium restriction, whereas essential hypertension in man is often favorably affected by both of these measures.

This contrast may point out a fundamental difference in the pathogenesis of these two types of hypertension. An understanding of this difference might shed light on the still mysterious basic derangement in all types of hypertension.

Summary. Arterial hypertension was produced in a group of rats by narrowing one renal artery. These hypertensive rats ingested large doses of a thiazide drug for a period of five weeks. During this period, the drug was completely ineffective for lowering arterial pressure. This is in striking contrast to the great effectiveness of thiazide drugs in alleviating essential hypertension in man. This contrast may point out a fundamental difference in the pathogenesis of these 2 types of hypertension. Moreover, this observation might prove to be clinically useful; hypertensive patients who get a good response to thiazide drugs alone would be more likely to have essential hypertension rather than renovascular hypertension. The inability of the thiazide drugs to alleviate renovascular hypertension in the rat is paralleled by a similar ineffectiveness of the low sodium diet.

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Antimicrobial Activity of Thiobenzoate and Its *O*-Fluoro- and *M*-Fluoro-Derivatives.* (28869)

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An earlier report from this laboratory showed that the antifungal peptide, Ro2-7758 (Hoffmann-LaRoche), was stimulatory to the yeast sulfate reductase system at low concentrations but inhibitory at higher concentrations(1). Even though some discrepancies were encountered in attempting to correlate this action with all aspects of the activity spectrum of Ro2-7758, it was concluded that the inhibitory effect on sulfate reduction may play a role in its antibiotic action. The suggestion was also offered that a search should be made for synthetic compounds which would inhibit this metabolic pathway which is unique in microorganisms, with an aim toward development of effective antifungal agents.

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The high sulfur content of Ro2-7758(2) prompted an investigation of the effects of certain sulfur-containing compounds on microbial growth, and an attempt to correlate any observed action with effect on the sulfate reduction system. The following is the result of studies with thiobenzoate and its *o*-fluoro- and *m*-fluoro- derivatives.

Materials and methods. All microorganisms were stock laboratory strains which had been maintained in this laboratory for several years. Tryptic soy medium and Sabouraud dextrose medium were used for cultivation of bacteria and fungi, respectively.

Thiobenzoic acid (TBA) was obtained from Aldrich Chemical Co., Milwaukee, Wisc. The fluorinated derivatives were synthesized by Hynes Chemical Research Corp., Durham, N. C. All 3 thiobenzoates are liquids at room