through their reaction with tissue and tissue fluid, may explain their low rate of translocation as compared to Ag^{111} oxide. Both insoluble compounds are suitable, due to their ability to be deposited and stored in requisite areas, for topical treatment of malignant conditions and perhaps also of some benign pathological tissue structures(5).

Poor vascularization and large amount of connective tissue in the scalp may account for relatively slow and scanty translocation of any compound from site of injection. Vice versa, rapid and copious translocation from the tail may be correlated with its high vascularization and low content of connective tissue.

It should be noted that according to our reports on Y^{90} chloride and Ag^{111} oxide(2,5) and our unpublished results with Ag^{111} iodide the pattern of translocation for an insoluble compound given topically was considerably modified by the presence of tumor tissue in the injected area: storage of the isotope in this area was considerably higher than in normal tissues due to occlusion of lymph channels and tissue spaces by growing malignant elements (and frequently also of blood vessels by hemorrhages). This is the rationale for therapeutic trial of above compounds in tumor-bearing mice which we are carrying out at the present time.

Summary and conclusions. 1) Data were obtained in mice on translocation of 5 radioactive silver Ag^{111} compounds at various intervals after injection into the tail by a previously described method of serial tail amputations and 24 hours after injection into the scalp. 2) Ag^{111} nitrate storage rate at site of injection was higher than for another soluble compound—Ag^{111} lactate, but lower than for 2 insoluble coarsely particulate compounds—Ag^{111} oxide and chloride; on the contrary, pick-up by liver and blood was highest for soluble compounds. 3) Translocation of each compound from the scalp followed the pattern of its translocation from the tail but at a much slower rate. 4) In the above experimental conditions the fate of various Ag^{111} compounds in the body of the mouse depended mainly a) on the physico-chemical properties of the compound (solubility, pH, ability to form colloidal complexes with tissue fluid and blood, size and tendency of insoluble particles to clump) and b) on biological conditions at site of injection. 5) The planned use of this method in tumor-bearing mice is presumed to be helpful for selection of the choice compound for local or systemic therapeutic application.

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Antihypertensive Properties of Furazolidone. (24621)

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Sustained diastolic hypertension is associated with progressive decrease in renal function and increase in cardiac and cerebrovascular complications(1). Effective reduction of blood pressure arrests this progressive vascular deterioration(2). Although potent vasodepressor drugs have been developed, intolerance to certain of their actions has prolonged the search for new therapeutic agents which may obviate these difficulties(3). Differing modes of antihypertensive activity are being explored to gain insight into pathogenesis of primary hypertension, thereby affording a more rational therapeutic approach. Recent observation that blood pressure might be reduced during initial clinical pharmacologic

FURAZOLIDONE

N-(5-nitro-2-furylidene)-3-amino-2-oxazolidone

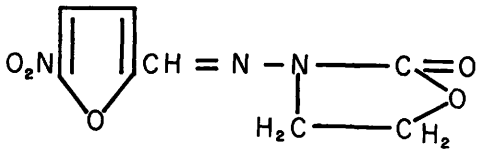


FIG. 1.

studies of furazolidone (Fig. 1) was unexpected(4). Furazolidone failed to reduce blood pressure in hypertensive rats (personal communication) and previously developed nitrofuran compounds were not found to be vasodepressor. The present study was undertaken to define any antihypertensive properties of furazolidone* and to explore its possible application and limitations in treatment of patients with hypertensive cardiovascular disease.

Materials and methods. Twenty-two ambulatory patients were studied. Patients with demonstrable secondary hypertension were excluded. Ten patients had mild, 10 moderate and one severe hypertension. In addition, one normotensive subject was included to differentiate hypotensive from antihypertensive action. The age range was 37 to 73 years with mean of 56.4 years. Fourteen patients were Negroes, of whom 9 were females and 5 were males. Of eight Caucasians, there were 5 females and 3 males. Each patient received a physical examination initially and a comprehensive history was taken. Clinical observations were repeated at weekly intervals throughout investigation. We recorded blood pressure and pulse rate in supine, sitting and standing positions. All recorded blood pressures were averaged for the control period and for period of effective drug administration (D). Initial laboratory examinations included complete blood cell count, urinalysis, blood urea nitrogen determination, x-ray of chest, electrocardiogram and stool culture. Blood cell count, urinalysis and stool culture were repeated bi-weekly. Tests of hepatic function and assays of serum electrolytes and blood urea nitrogen were repeated at intervals in certain patients. A matched placebo was administered throughout control period. Furazolidone tablets of 100 mg were then substituted in divided doses, from 300 to 1,250 mg daily. Duration of treatment with the drug was from 1 to 6 months. After additional period of placebo administration, 3 patients received a second course of furazolidone therapy.

Results. Twenty of the 22 patients studied had a reduction in mean arterial blood pressure (calculated as diastolic pressure plus one-third of pulse pressure) averaging 28 mm Hg, range 13 to 44 mm Hg (Table I). Systolic and diastolic pressures were decreased by average of 42 and 20 mm Hg respectively. An example of antihypertensive response is seen in Fig. 2. It was necessary to withdraw therapy because of side effects, in the remaining 2 patients before any antihypertensive action occurred. Two patients had an orthostatic blood pressure reduction. Several others complained of orthostatic weakness and dizziness which was not correlated with postural hypotension. The normotensive individual experienced hypotensive response of calculated mean blood pressure of 23 mm Hg.

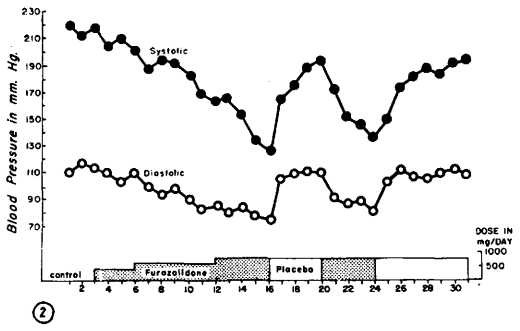
TABLE I. Effect of Furazolidone upon Blood Pressure.

Age	R	Sex	Blood pressure* Control	D	Change	Effective dose, mg	Onset of B.P. response, wk
67	W	♂	135	107	−28	800	2
56	N	♂	158	115	−43	1000	3
† 49	N	♂	127	95	−32	1000	4
† 62	N	♀	128	97	−31	800	3
65	W	♀	127	106	−21	300	4
‡ 57	N	♀	129	103	−26	600	3
† 56	N	♀	130	114	−16	800	3
44	N	♀	128	105	−23	800	4
53	N	♀	145	101	−44	800	4
‡ 54	N	♀	139	106	−33	400	5
‡ 55	N	♂	129	111	−18	600	3
49	W	♂	134	112	−22	800	5
70	W	♀	140	127	−13	800	4
45	N	♀	128	88	−40	800	1
73	N	♀	134	105	−29	800	4
†§73	W	♀	136	121	−15	800	4
‡ 52	W	♂	127	85	−42	1000	7
†§65	N	♂	123	103	−20	800	6
46	N	♂	102	79	−23	800	7
‡ 71	W	♀	126	105	−21	1000	1

* Calculated MAP.
† Side reactions necessitated stopping drug.
‡ Developed tolerance.
§ Orthostatic effect.
‖ Normotensive.

The average daily dose required for maxi-

* Furnished as Furozone® by Eaton Labs.



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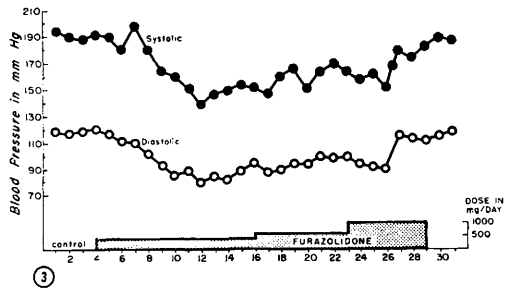

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FIG. 2. Blood pressure response to furazolidone.
FIG. 3. Development of tolerance to furazolidone.

mal effect was 775 mg with range of 300 to 1,000 mg. Attempts to reduce dosage after satisfactory effect was achieved, resulted in elevation of blood pressure. Initial antihypertensive action was manifest as early as one week, upon reaching an effective dose level; maximum response was usually attained in 3 to 4 weeks, occasionally somewhat later. Five patients became refractory to hypotensive action during our study (Fig. 3). This occurred even though dosage was increased to 1,250 mg daily. After withdrawal of drug and substitution of placebo, the blood pressure returned to its previous high levels in average of 4 weeks, with range of 1 to 8 weeks.

Furazolidone is considered to be excreted in part in the urine largely as chemically altered products. Therefore, color of urine became a characteristic amber at doses of 400 mg or more daily, intensity of color proportional to dose. This afforded an excellent verification that medication was taken as prescribed. Similarly, yellow tint of sclera developed in several patients. Since many were Negroes, the possibility of some yellow discoloration of skin could not be excluded. Laboratory studies failed to demonstrate hepatic dysfunction or hemolysis.

Body weight loss averaging 6.3 lb occurred in 12 patients, 8 of whom complained of anorexia. Nausea and vomiting were present in about one-third of patients. Other gastrointestinal effects included abdominal cramps and diarrhea in 4 and 3 patients respectively. Changes in stool flora were produced in one-third of the patients. These occurred as early as 2 weeks after initiation of therapy and included complete suppression of normal flora, appearance of Clostridia, increase in *Streptococcus viridans* and *S. hemolyticus* or replacement of normal flora by any 1 or all of aforementioned bacteria. Generalized pruritis occurred in 2 patients. Purpura, predominantly involving the 4 extremities with small confluent lesions, occurred in one patient 2 weeks after increasing the dose to 600 mg from previous level of 400 mg daily. Peripheral blood smear, platelet count and coagulation studies were normal. The purpura resolved in a few days following discontinuation of furazolidone. Anemia developed in one Negro female, improved on withdrawal of furazolidone and recurred upon reinstitution of therapy. Transitory hemic eosinophilia was observed in 2 patients, but could not be definitely related to the drug. Other infrequent complaints included a feeling of anxiety, cardiac palpitation and twitching of fingers. No abnormalities of serum electrolytes, blood urea nitrogen, urinalysis nor hepatic function were observed.

Discussion. The magnitude and consistency of blood pressure reduction achieved by furazolidone is of considerable clinical import. Both systolic and diastolic pressures were reduced, the former more than the latter, resulting in diminution of pulse pressure. The action appeared to be hypotensive rather than purely antihypertensive.

Of particular interest is the possibility that furazolidone may reduce blood pressure by a mechanism not evoked by currently available drugs. Although some evidence of orthostatic effect was observed, absence of other indications of sympathicolytic or parasympathicolytic action make ganglion blockade an unlikely principal explanation for the effect. The possible correlation of body weight loss with

blood pressure reduction was considered. Of the 12 patients who lost 5 pounds or more, one-half evidenced a temporal relationship. Time curves did not coincide in the others. Upon discontinuation of the drug, weight was often regained more slowly than blood pressure was reelevated. In approximately two-thirds of the patients, change in stool flora coincided with the hypotensive effect. However, in one of these patients, a second course of furazolidone therapy failed to show such relationship. Consequently, it is not yet possible to draw conclusions regarding possible mechanism of hypotensive action.

Dosage required to lower blood pressure optimally in this study was considerably higher than that which has been recommended for enteric antibacterial therapy. At such high doses, the adverse effects, most frequently gastrointestinal in nature, definitely limit application of the drug in treatment of hypertension. Development of a refractory state to the vasodepressor action is a problem which has not been solved by increasing the dose. However, furazolidone may represent a new point of departure from which other derivatives may retain potent antihypertensive action dissociated from the aforementioned limitations.

Conclusions. Furazolidone in adequate dosage exerts a significant hypotensive action. The exact mechanism whereby this occurs remains obscure. Frequency and severity of adverse effects and development of a refractory state limit application of the drug in treatment of patients with hypertension. It is to be hoped that derivatives may dissociate the hypotensive from the unwanted effects.

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Effect of Antihistaminic and Antiserotonin Drugs on Vascular Responses to *E. coli* Endotoxin in the Cat.* (24622)

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Devices by which endotoxin causes shock and death are only partly understood. The resemblance of its early vascular effects in certain species(1) to changes seen in anaphylaxis (2) has suggested that there may be certain mechanisms common to both situations. Since histamine and 5-HT (5-hydroxytryptamine) are known to be released in anaphylaxis(3) it seemed possible that they may also be set free in reactions to endotoxin and that antihistaminic and antiserotonin drugs might therefore block some effects of endotoxin. Chlorpromazine, which has both antihistaminic and adrenergic blocking activity(4) has been shown to protect mice against lethal effects of endotoxin(5). Dibenzyline has also been found to have a protective effect(6,7). In the present study, a combination of dibenamine and pyrilamine blocked the *immediate* systemic hypotensive effect of small doses of endotoxin in cats.

Methods. In the cat, endotoxin causes a sharp rise of PAP (Pulmonary artery pressure) and of total pulmonary vascular resistance. This is followed by a decline in BP (systemic arterial blood pressure) from which there is usually a temporary recovery(8). Cats were anesthetized with intraperitoneally injected sodium pentobarbital (35 mg/kg). After cannulation of the trachea and carotid artery, the chest was opened to permit insertion of a polyethylene catheter into the pulmonary artery. The PAP and BP were meas-

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