INTRODUCTION:
A Statement of the Present Study.

Since peripheral resistance is the function of the contractile state of arterial smooth muscle cell whose innervation is mainly adrenergic, research on antihypertensive therapy has been focused on the inhibition of sympathetic nervous system. However, it has been impossible to establish a cause and effect relationship between malfunction of the autonomic nervous system and hypertension (Reader, 1970).

Only part of the activation of arterial smooth muscle is neurogenic, the remainder being myogenic (Van Breemen et al., 1972). A promising approach to the alleviation of hypertension is thus to understand and then to modify the cellular control system which regulates the contractile state.

Although the rat has been extensively utilized as an experimental model in hypertensive studies, the understanding of the vascular smooth muscle physiology and pharmacology has been mostly due to in vitro studies utilizing the isolated rabbit thoracic arterial strip, which is generally assumed to be a representative model for other species also. Despite the fact that there are species variations in vascular and other smooth muscle reactivity to various contractile and relaxant agents, the excitation-contraction and coupling was thought to be unique until recent pharmacological studies (Hurwitz
et al., 1969; Fleisch et al., 1970; Maling et al., 1971; Patil et al., 1972; Burnstock et al., 1970). Further, unlike in rabbit aorta, reserpine failed to induce supersensitivity in rat aorta even to NE (Krishnamurty and Grollman, 1972).

The present study was taken up to investigate the physiology and pharmacology of the vascular smooth muscle in vitro as given under the following: 1) to verify whether the innervation of this muscle is in any way related to direct action of tyramine and increased sensitivity of this muscle to NE. This was solved by studying antagonism of these two agents against phentolamine before and after reserpine treatment for depletion of catecholamines to avoid indirect component by the release of endogenous amines and cocaine treatment for the inhibition of amine uptake of the adrenergic neuronal endings. Further, 6-hydroxydopamine (6-OHDA) and desmethyl imipramine (DMI) were also used for the chemical sympathectomy and for the inhibition of uptake of exogenously added sympathomimetic amines, respectively., 2) to verify whether the reserpine pretreatment of rats would induce supersensitivity in vascular smooth muscle to various contractile agents. This was attempted by treating rats with a wide range of dose schedules of reserpine (0.3 mg/kg/day for 1 - 3 days to 5 mg/kg/day for 2 days)., 3) to verify whether the contractile nature of this muscle to various contractile agents is dependent upon external Ca++ utilization. This was attempted by studying differential antagonism against NE, 5-HT and KCl of SKF 525-A which specifically inhibits the Ca++ utilized
in K-induced contractions and by incubating muscle in Ca++ and Na+-
free solution by testing for the contractile capacity of this muscle
to K and NE., 4) to verify whether separate receptors for 5-HT
and sympathomimetic amines are present in this muscle and whether
5-HT and sympathomimetic amines act mutually on alpha-adrenergic
receptors. This problem was attempted by studying antagonism of
sympathomimetic amines and 5-HT against two specific competitive
antagonists - phentolamine, an alpha adrenergic receptor antagonist
(for sympathomimetic amines) and BOL, a 5-HT receptor antagonist., 5)
to study whether 5-HT has an influence on this muscle to increase the
sensitivity to NE. This was attempted by incubating muscle in 5-HT
at subthreshold concentration before and after determining dose-
response curves to NE., 6) to study whether the reactivity of the
acutely hypertensive vascular smooth muscle to contractile agents
(NE, 5-HT and KCl) is in any way different from chronically hyper-
tensive and normotensive muscles. This problem was attempted by util-
izing EDTA and SKF525-A against NE, 5-HT and KCl and correlating in-
creased sensitivity of the muscle with the presence of pressor action
of plasma from these rats as determined on rabbit ear artery perfu-
sion pressure., and 7) to verify whether the pressor activity of
the acutely hypertensive plasma (nephrotensin) is in any way dif-
ferent from angiotensin I and II. This was attempted by studying
pressor activity of nephrotensin against angiotensin I antibody and
sensitizing activity to Angio II and NE on rat blood pressure and
rabbit ear artery perfusion pressure.
It was expected that this study would increase our understanding of muscle contraction and might unfold some of the mysteries involved in supersensitivity which occurs in hypertension (Hinke, 1965b; Kalsner et al., 1971; Bandick and Sparks, 1970).