STUDIES ON THE ROLE OF ADRENERGIC VASOCONSTRICTION IN THE DEVELOPMENT OF SHOCK

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by

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This thesis is affectionately dedicated to:

My fiancée, Constance English who in the past four years has manifested the major requisite for a scientist's wife -- patience.

My parents, Theophil and Christine, for their whole-hearted moral and material support throughout my academic career.

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Abstract

The major purpose of the present studies was to assess more completely the role of vasoconstriction and of reduced effective regional blood flow in the genesis of shock.

The protection provided by phenoxybenzamine against the development of shock is related to its prolonged and highly specific adrenergic blocking activity. In addition to reducing vasoconstriction due to sympathetic nervous system hyperactivity accompanying shock, phenoxybenzamine may also provide an increased plasma volume and a more favorable distribution of the available blood. Both the reactive β-halogen and an appropriate aromatic group (phenoxyisopropyl, benzyl, etc.) have been shown to be necessary structural components for this activity.

Investigation of the cardiovascular and lethal effects of *Escherichia coli* endotoxin indicates that peripheral adrenergic mechanisms are intimately involved in these effects. The results support the concept that deleterious effects of endotoxin in shock probably are due to exaggeration of existing vasoconstriction in an already compromised organism.

The rate of total-body uptake of radiorubidium (Rb^{86}) is delayed considerably during shock. This is probably due to delay in equilibration between plasma and extracellular fluid. The relation of blood flow to uptake of locally-administered Rb^{86} was investigated in the vascular beds of

hind limbs and ileum in dogs. The flow-uptake relation for Rb^{86} in the vascular beds of the hind limb was affected very little by shock-inducing procedures. However, in the ileum Rb^{86} uptake was considerably depressed even at low flow rates throughout the period of norepinephrine infusion, even prior to the development of shock by these infusions. This decreased uptake also occurred during the normovolemic phase of hemorrhagic shock. These changes indicate that a decreased fraction of the total organ blood flow was traversing vessels from which exchange with tissues occurred readily. The normal flow-uptake relation was maintained throughout in animals protected with phenoxybenzamine. Thus, a major component on the protection provided by phenoxybenzamine may be prevention of the deleterious redistribution of intra-organ blood flow during shock, permitting more effective nutrition of compromised tissues.

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