THE ROLE OF CERTAIN VASOACTIVE SUBSTANCES IN THE CONTROL OF THE PERIPHERAL CIRCULATION IN MAN.

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This thesis examines the role of several vasoactive substances, especially serotonin, in the control of the peripheral circulation in man and includes studies of the capacity and fluid exchange properties of the peripheral circulation. This division of the systemic circulation can be subdivided into three principal functional areas:

(1) the resistance vessels, mainly the arterioles
(2) the exchange vessels, exchange of solutes and water occurring across capillary walls, and,
(3) the capacity vessels, the veins.

The peripheral circulation is involved in two sets of control mechanisms, one local and the other general. On the one hand it plays a part in the supply of nutrients and removal of waste products according to the local needs of each tissue, and on the other it is involved in generalized adjustments such as those of cardiac output, systemic blood pressure and body temperature. At both of these levels the necessary adjustments of the circulation through a given tissue are effected by the action on the smooth muscle of the resistance and capacity vessels of hormonal or chemical agents and by nervous influences, which act ultimately by way of chemical transmitters.

The effects of a number of these agents on the peripheral

circulation have been investigated intensively and the mechanisms of action of such vasoactive substances as adrenaline, noradrenaline, serotonin and angiotensin are becoming clarified. However, under physiological conditions the vessels will often be exposed to the effects of two or more of these agents acting simultaneously and little is known of the ways in which they may interact with one another. Work described in Section 2 of this thesis examines the actions of some of the naturally occurring vasoactive substances on the resistance vessels and relates ways in which their actions may be influenced by the effects of others and by the presence or absence of sympathetic innervation.

Emphasis throughout is placed on the circulation in the skin and muscle of the upper limb since the limb vascular beds are the most readily accessible to methods of measurement which do not themselves interfere greatly with the circulation. Most studies have involved indirect measurements of hand or forearm blood flow by the technique of venous occlusion plethysmography, using either water displacement or electro-capacitance plethysmographs. In general, local effects of the various vasoactive substances have been studied by infusing them intra-arterially into the main artery supplying the vascular bed. Relatively high concentrations can thus be given locally but the substance is so diluted when it reaches the general circulation that it has no widespread effects. The circulation

through the corresponding vascular bed of the opposite limb can thus be used as a control. General effects of the vasoactive substances were assessed by intravenous administration. General effects, however, are often more difficult to interpret since the effects of the vasoactive substances are often complicated by reflex cardiovascular effects and respiratory and emotional effects on the subject. Thus a preference is shown for the intra-arterial studies since the effects of the vasoactive substances are more clearly apparent.

The studies of the peripheral vascular effects of serotonin, angiotensin and noradrenaline were followed by a study of the role of a number of vasoactive substances (especially acetylcholine) in the phenomenon of post-exercise hyperaemia of the resistance vessels of skeletal muscle (Section 3). The search for the elusive vasoactive substance or substances responsible for this well recognized pheomenon has absorbed the interest of investigators for many years. In addition to the study in man, the study of post-exercise hyperaemia was extended to animal work (the sheep) since it seemed appropriate to extend the search for vasoactive substances to lymph, and this was not feasible in man. Finally, in the sections on the resistance vessels the effects of ethyl alcohol were studied as an example of a vasoactive substance which is not a naturally occurring one (Section 4).

In Sections 5 and 6 are described studies on venous tone and on capillary filtration which were undertaken at the University of Southern California, while all the previous investigations in Sections 2-4 were performed at the University of Adelaide. The study of venous distensibility in normotensive and hypertensive patients and the effects of antihypertensive treatment on the latter provided data on normal and abnormal responses of the capacity vessels. Capillary filtration rate and capillary filtration coefficient were measured plethysmographically and the effect of adrenaline iontophoresis (to the skin) on the rate of accumulation of tissue fluid in the forearm was assessed,

Throughout all these studies it was apparent that the general (central) and local control of the peripheral vessels was influenced in a highly specific manner by the interaction of various hormonal, chemical and nervous factors.