URINARY CATECHOLAMINE METABOLITES IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS AND THE EFFECT OF BETA ADRENERGIC RECEPTOR BLOCKING DRUGS ON THE BLOOD PRESSURE AND URINARY CATECHOLAMINES

THESIS

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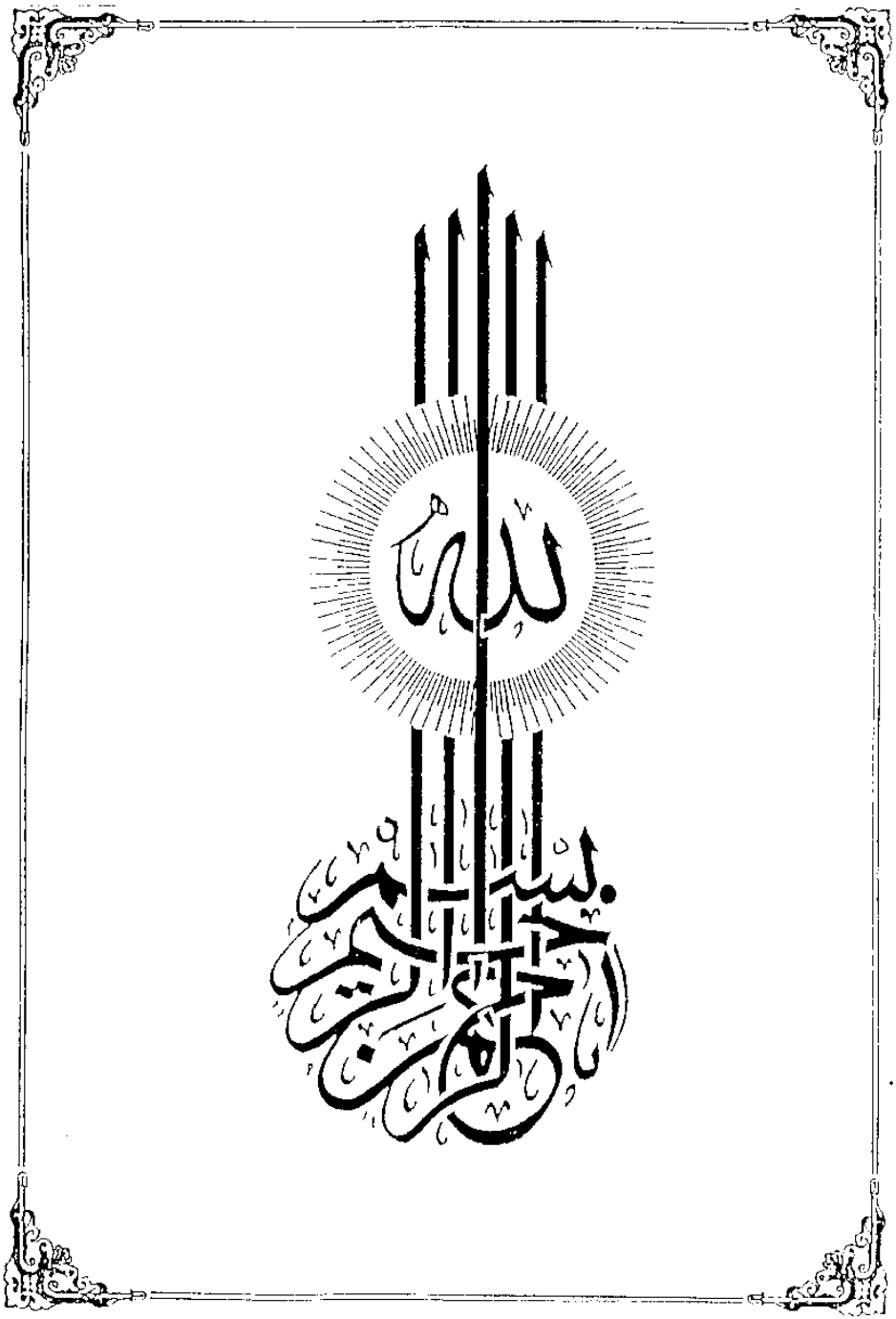

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CONTENTS

INTRODUCTION

HYPERTENSION

Importance, incidence and complications :

High blood pressure, by reason of its prevalence and because of the gravity of its sequelae, ranks as one of the major medical problems of the present time. Statistics show that hypertension is indeed extremely widespread; so while in young adults, only 5% suffer from hypertension, in the fifth decade of life its percentage is already 10-20%, and in persons over fifty, the incidence rises to 20 - 30 % (Master et al 1952).

Patients with elevated arterial pressure tend to die prematurely (Pickering 1972) Hypertension is the most significant known risk factor in the development of strokes (Kannel et al 1970), congestive heart failure (Mckee et al 1971) and renal insufficiency (Laragh 1972), and in induction of atherosclerotic phenomena and arterial lesions in general. (Pickering 1972). Hypertension is also one of the most important predisposing factors in coronary heart disease and myocardial infarction, appearing at least as important as any of other risk factors such as hyperchlolesterolaemia (Laragh 1972).

Concering the mortality due to hypertension, in 1962 this disease accounted for [illegible] (Fahr) of all deaths in the U.S.A. [illegible] of age. In England and Wales, in 1953 hypertension accounted for 4% of all deaths ([illegible]% of cardiovascular deaths) (Paul Wood 1966). More recent data are those collected by the Society of Actuaries (Schoonberger 1971). It shows the increasing mortality ratio which can be assigned to relatively modest increase in blood pressure. Thus men with casual blood pressure of 140/90 mm.Hg have 50% increase in mortality if followed for 20 years, compared to expected incidence. This figure rises to over 100 % in those people who have blood pressure of 160/100 mm.Hg. Because of the importance of high blood pressure, it is essential to discuss first the normal blood pressure, how it is maintained and the different physiological factors which might affect it.

Factors that determine and maintain the normal blood pressure : (Best and Taylor 1967)

(1) The pumping action of the heart :-

The means by which the cardiac contraction exerts its effect upon the arterial pressure, is obviously through the quantity of blood which it is capable of discharging into

the aorta in a unit period of time, i.e., upon the output of the heart per minute or stroke volume times heart rate. When more blood is forced into the already filled arterial system, it cannot escape at once from the system in the same amount as it is thrown into the aorta, so the arterial walls become stretched. The pressure rises until the velocity of flow through the arterioles is great enough to balance again the outflow from the system with the inflow. So the increase of the cardiac output due to any factor causes an increase in both the systolic and diastolic pressures, but the systolic is affected more than the diastolic.

(2) The peripheral resistance :-

The peripheral resistance is dependent upon the caliber of the small vessels, mainly of the arterioles and, to a less extent, of the capillaries and the viscosity of blood. The total peripheral resistance in man can be calculated from the mean blood pressure (M) and the cardiac output (C.O.P.), since all the blood entering the aorta must of course pass through the peripheral vessels. This relationship can be expressed in the following equation :-

$$R \text{ (peripheral resistance)} = \frac{M(\text{mmHg}) \times 1332}{C.O.P.(\text{ml/sec})} = \frac{\text{Dynes. seconds}}{\text{cm}^5}$$

1332 is a figure for conversion of pressure to dynes. The peripheral resistance amounts normally to from about 600 to 2,000 absolute unites in man, but may be over 5,000 in arterial hypertension. The increase of peripheral resistance affects the diastolic more than systolic blood pressure.

(3) The capacity of blood in the arterial system :

In any closed system of rigid tubes, fluid must fill it to capacity in order that a pressure can be developed within it. The arterial walls are distensible and elastic, and a certain degree of stretching of these must occur before any considerable pressure is created. The arterial system must be over filled, and the greater the extent of over filling, the greater will be the blood pressure.

(4) Viscosity of blood :

Since the viscosity of blood mainly depends on the corpuscular content, it shows only minor variations during the course of the day.

(5) The elasticity of the vessel walls :

This is concerned mainly with the origin and maintenance of the diastolic pressure and sustaining the mean pressure at a higher level, than would be possible in a rigid system under otherwise identical conditions.

The elasticity of arterial tissue does not come into play to any notable extent with a pressure below 30 mm. Hg. Below this level there would be little stretching of the walls of the arteries which would then behave like a system of rigid tubes. At the usual diastolic pressure that exists, however, the walls are stretched by virtue of their elasticity and tend to recoil against the distending force. As the content of the ventricle are thrown into the already over-filled system during systole, the added pressure which is then exerted upon the vascular walls causes their further distension. After the completion of systole, the elastic walls rebound and, pressing upon the blood within their embrance, force it onwards through the peripheral vessels. In other words, the arterial lumen returns to its previous diameter, and the energy that had been stored up during the stretching of the elastic tissue is in this way gradually expended during diastole. The elastic recoil of the arterial wall thus acts in a sense as a subsidary pump to drive the blood onwards in a continous stream between the heart beats, other-wise the pressure will fall to zero after each systole. So the elasticity of the vascular walls and the peripheral resistance are both essential for the maintenance of the diastolic pressure.

Physiological variations of the blood pressure :

The important physiological factors which cause variations in the normal blood pressure are :-

1- Diurnal variations :

Slight diurnal variations in the blood pressure from 5 to 10 mmHg systolic might occur, the peak being in the afternoon and the lowest level in the early hours of the morning.

2- Age and sex :

Age exerts a definite influence upon the blood pressure levels . At birth the systolic pressure measures from 20 to 60 mmHg with an average of 40 mmHg. It rises rapidly, however and has an average value of about 70 mmHg at the end of a fortnight, and 80 mmHg at the end of a month. A slow steady rise takes place from this time until about the 12th year when it averages 105 mmHg. With the onset of puberty, a more sudden rise occurs which in boys reaches 120 mmHg about the age of 17. A steady though not great rise in blood pressure from adolescence to old age is the rule in health, the average for the ages of 60 being about 140 systolic pressure and 87 diastolic. In women up to the time of menopause the systolic pressure is from 4 to 5 mmHg lower than for men of the same age.

At menopause however there is a somewhat abrupt rise and the pressure remains a little [illegible] this change.

3- Effect of food :

The systolic pressure is influenced to a small but definite extent by meals. A rise from 5 to 8 mmHg is the usual effect, and this lasts for an hour or so. However there is little change in diastolic pressure by meals. If anything, it is reduced, presumably as a result of vasodilatation in the digestive organs.

4- Sleep :

Quiet, restful sleep may be accompanied by a fall of from 15 to 30 mmHg in the systolic pressure. The fall is most marked during the first hours, rising gradually again after this until the time of waking.

5- Exercise :

Exercise if of a strenuous nature, has the most powerful effect upon the arterial blood pressure. During muscular effort, the systolic pressure commences to rise and may reach a height of 180 or 200 mmHg. The diastolic pressure shows a less pronounced rise (100 to 110 mmHg) and so the pulse pressure is increased.

6- Effect of posture :

The diastolic pressure is higher in standing than in the sitting position and lower in frequency. This change is found to occur whether the position change is brought about actively or passively and is evidence of overcompensation for the gravity effect. The systolic pressure usually rises but to a less extent than the diastolic, so the pulse pressure is reduced. Pressures however, taken at as short an interval as 10 seconds after the erect position has been assumed, show that the initial effect is a fall of from 6 to 22 mmHg in systolic pressure. This is sufficient to stimulate the carotid sinus and aortic mechanisms and cause increased vascular tone with consequent compensatory rise in pressure. Compensation is usually complete within 30 seconds.

The important pressure-regulating systems :

1- The renin angiotensin-aldosterone system : (Gantt 1967)

A decrease in pulse pressure, mean arterial pressure, or renal blood flow causes the cells of the juxtaglomerular apparatus (which includes the macula densa by definition) of the kidney to release the enzyme renin. Renin acts on alpha 2 globulin made by the liver (renin-substrate) to produce