ESSENTIAL HYPERTENSION: A REVIEW OF RESEARCH ON SOME ASPECTS OF A PSYCHOSOMATIC DISORDER

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PREFACE

This thesis is a review of research literature on the subject of essential hypertension. Papers have been selected from the areas of clinical psychology, psychophysiology, neurophysiology, the physiology of the circulation, and biochemistry. The selection of papers has been made with the intent of presenting as broad a view as possible of the character and etiology of hypertension. Critical evaluation of published research in terms of methodology and validity of findings has been sacrificed to this primary objective of breadth and cohesion. The omission is intentional not only because such an approach would be beyond the scope and intent of this paper, but also because such a critical effort made upon so large an area of experimental research would prove both innept and presumptuous.

Choice of publications was made on the basis of information contained in the listings of the Cumulative Index Medicus (CIM), published by the National Library of Medicine. The facilities of the following libraries were used in the course of research: Oklahoma State University Library, Stillwater; Library of the School of Medicine, University of Oklahoma, Oklahoma City; Library of the School of Medicine, University of Michigan, Ann Arbor; Shiffman Medical Library, Wayne State University School of Medicine, Detroit.

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CHAPTER I

DEFINITION OF THE PROBLEM

Introduction

Those aspects of essential hypertension chosen for discussion in this paper will be introduced as several kinds of interaction. It will be seen that there is interaction between those brain mechanisms that govern emotional, motivational, and attitudinal states and the neuroendocrine secretions that determine the integrity of the arterial network. There is an interaction between central state and the delicate buffer mechanism for control of systemic blood pressure that operates at the vascular confluence of brain and peripheral circulation, the carotid sinus and the aortic arch. Although there is a relative paucity of information on motor behavior and circulation in skeletal muscle in the hypertensive human, there are enough data from animal research in this area of physiology to provide a basis for conjecture on the role of striated muscle activity in human cardiovascular regulation. Any one of these systems may develop sufficient deviation from normal functioning to initiate elevation of blood pressure, or they may do so by acting in concert.

The psychology of functional disorders has been studied exhaustively and yet continues to elude satisfactory definition. It is possible, however, to correlate several kinds of evidence to arrive at a

definition for hypertension that seems plausible. This evidence will come from studies of the hypertensive personality, from research on the physiological specificity of emotional response, and from evidence, derived principally from animal studies, that certain emotional behaviors inevitably accompany sympathetic arousal under acute experimental conditions.

It is hoped that this view of essential hypertension from several aspects may serve to illustrate how emotional, autonomic, and motor behavior can combine to produce disease.

CHAPTER II

THE ROLE OF NEUROHUMORS, HORMONES, PEPTIDES, AND ENZYMES IN THE PATHOLOGY OF ESSENTIAL HYPERTENSION

The Pressor Response

Essential hypertension has three developmental stages. The first of these stages is the "diastolic reaction", or pre-hypertensive state, in which diastolic blood pressure is abnormally labile (Hambling, 1952). Benign essential hypertension, the subject of concern to this thesis, is also considered labile. In this stage of the disease, diastolic blood pressure remains fixed at a level somewhat in excess of 95 mm. Hg and hypertrophic alterations commence in the arterial system (Hambling, 1952) and in the left ventricle of the heart (Frolich, 1973). Malignant hypertension is characterized by a fixed level of diastolic blood pressure well above 95 mm. Hg and by severe pathology of the heart, the kidneys and the blood vessels (Hambling, 1952).

Morphologic changes in the cardiovascular system are inextricably related to chronically elevated blood pressure. Yet, it must be emphasized that both conditions are end-results of an essentially adaptive physiological mechanism: the pressor response. In its normal functioning, in both normal and hypertensive persons dealing with the exigencies of daily life, the cardiovascular system responds to sympathetic vaso-

motor activity with quite considerable fluctuations in blood pressure (Bevan, Honour, and Stott, 1969; Charvat, Dell, and Folkow, 1964; Hinman, Engel, and Bickford, 1962). The point at issue is how this flexible and life-supporting response becomes chronic, maladaptive, and ultimately life-threatening.

The Neural Anatomy of the Pressor Response

The pressor response is a mass discharge of the sympathetic branch of the autonomic nervous system. Centrally mediated, this response is the vasomotor expression of psychological drives that originate, in large part, from subcortical regions of the brain (Roberts, 1970; Zanchetti, 1970). Neurons in the hypothalamic-preoptic area, the limbic system, and the trajectory of the medial forebrain bundle that are specific to visceromotor, somatomotor, and sensory processes are also specific to emotionally motivated behavior (Folkow and Rubinstein, 1965; Flynn et al., 1970; Roberts, 1970; Wasman and Flynn, 1962; Zanchetti, 1970).

The hypothalamus, among all lower brain structures (Netter, 1958), has the major influence upon cardiovascular reactions as these relate to behavior (Bard, 1960; Nauta, 1972; Zanchetti, 1970), although its function in this regard is modulated by the carotid sinus/aortic arch inhibitory reflex (Bartorelli et al., 1959; Bizzi et al., 1961) and by the activity of the reticular formation (Malliani et al., 1963). When the defense reaction in the cat is evoked by electrical stimulation of the perifornical and medial forebrain bundle region of the postero-lateral hypothalamus (Akert, 1961; Wasman and Flynn, 1962; Zanchetti, 1970), the reaction combines the pressor response, an alerting response, affective

display of either alarm or rage, and final escalation into escape or attack behavior with full engagement of the skeletal musculature (Abrahams and Hilton, 1958; Abrahams, Hilton, and Zbrozyna, 1960; Abrahams, Hilton, and Zbrozyna, 1964; Baccelli et al., 1965; Baccelli et al., 1968; Folkow and Rubinstein, 1965; Folkow et al., 1968; Gloor, 1954; Hess, 1928; Zanchetti, 1970; Zanchetti et al., 1972).

Defined ever more precisely by numbers of investigators over many years, the pressor response is now understood to involve vasoconstriction in the intestines, the kidneys, and the skin, accompanied by elevation of blood pressure, increase in cardiac output, (heart rate and stroke volume), and inhibition of intestinal and gastric motility (Abrahams and Hilton, 1958; Anderson and Brown, 1967; Cannon, 1928; Eliasson et al., 1951; Folkow, 1962b; Folkow and Rubinstein, 1965; Folkow et al., 1968; Hess, 1954; Hess and Brugger, 1943; Masserman, 1943; Morpurgo, 1968; Ranson and Magoun, 1939; Rosen, 1961; Wasman and Flynn, 1962). Vasoconstriction of the blood vessels in skeletal muscle occurs as part of the pressor response when the body musculature is restrained or inhibited rather than actively mobilized under circumstances that call for defensive overt behavior (Baccelli et al., 1968). Muscle vasodilatation is concomitant, however, with vasoconstriction in the intestines and skin (Abrahams and Hilton, 1958; Eliasson et al., 1951; Golenhofen, 1968; Uvnas, 1960a; Uvnas, 1960b; Zanchetti et al., 1972). However, because fluctuations in blood flow in skeletal muscle are more the result of vasodilator than of vasoconstrictor nerve influence (Golenhofen, 1968), muscle does not, in contrast to viscera and skin, provide a reliable indicator of the pressor response (Bhagat, 1971; Delius et al., 1972; Rothe, 1966a; Rothe, 1966b).

Internal Secretions and the Pressor Response

There are three different kinds of substances internally secreted during sympathetic arousal that directly affect the peripheral circulation. These will be described as (a) the acetic acid ester of choline, acetylcholine; (b) the catecholamines, epinephrine and its precursor, norepinephrine; and (c) the polypeptide, angiotensin amide II. Of the four substances, norepinephrine and angiotensin II are of greater importance in essential hypertension; norepinephrine because it is both a potent and pervasive vasoconstrictor and a mediator of both central and peripheral neural processes; angiotensin II, because it is also a vasoconstrictor, and because its activity contributes to the coordinated functions of the kidney and the adrenal cortex. The two substances are important because there is a synergetic relationship between the nervous and hormonal functions that are controlled by norepinephrine, and the renal pressure reflex in which angiotensin II plays a part. Finally, they are important because each of these potent blood-borne messengers may have some abnormality in its metabolism that could contribute to the disease pathology. It must, however, be stressed that although these two secretions are demonstrably vasoactive, neither one, nor any other known secretion, is a mediator of hypertension in the sense of being a pressor substance found exclusively in the circulating plasma of hypertensive organisms. No such substance has been found (Grollman, 1972).

Acetylcholine

Acetylcholine is the cholinergic neurotransmitter of the preganglionic fibers of the sympathetic and of the pre- and postganglionic

fibers of the parasympathetic nervous systems. Its action is important in sympathetic mobilization for two reasons: (a) it is the neurohumor which mediates the release of epinephrine from the adrenal medulla; (b) it is the neurohumor secreted from sympathetic cholinergic vasodilatory fibers contained within peripheral sympathetic nerves (Eliasson et al., 1951; Grollman, 1969; Uvnas, 1960a; Uvnas, 1960b). These fibers originate in the motor cortex, the premotor cortex, the cingulate gyrus, and in the principal integrating center of the vasodilatory system, the anterior hypothalamus, through which all these fibers pass (Abrahams and Hilton, 1958; Abrahams et al., 1964; Eliasson et al., 1951; Folkow, 1962b; Folkow, Johansson, and Oberg, 1959; Folkow, Heymans, and Neil, 1965; Guyton, 1966; Rosen, 1961; Uvnas, 1960a; Uvnas, 1960b). They project exclusively to the precapillary sphincters and to the arterioles in skeletal and cardiac muscle (Abrahams et al., 1960; Bolme, Ngai, and Rosell, 1967a; Cobbold et al., 1963; Folkow, Mellander, and Oberg, 1961; Folkow et al., 1965; Mellander, 1960; Rosell and Uvnas, 1962; Tower, 1931; Uvnas, 1960a; Uvnas, 1960b).

Epinephrine

The catecholamine, epinephrine, is an adrenal medullary hormone. It is secreted from the chromaffin cells of the adrenal medulla in response to stimulation by sympathetic cholinergic preganglionic fibers (Rothe, 1966a). These cells are, therefore, modified sympathetic postganglionic neurons that are stimulated to secrete epinephrine from their intracellular granules by acetylcholine (Milnor, 1974; Rothe, 1966a).

Epinephrine produces profound metabolic and nervous effects by its acceleration of metabolic rate, heart rate, and liver glycogenolysis,

its stimulation of cardiac output (Grollman, 1969; Guyton, 1966), and its facilitation of synaptic transmission (Rothe, 1966a). The hormone constricts the blood vessels of the mesentery, the kidney, and the spleen, but it produces vasodilatation of the heart, liver, and skeletal muscle vasculature (Milnor, 1974). Skeletal muscle response to epinephrine has, however, been shown to be dose-dependent. Celander (1954) produced near maximum vasodilatation at low concentrations of infused L-epinephrine (0.05 ug./kg./min.) and vasoconstriction at higher dose levels in the decentralized blood vessels of the leg muscles in the cat. The cross-over point from vasodilatation to vasoconstriction was 2 ug./kg./min. infusion rate.

Norepinephrine

Norepinephrine is both an adrenal medullary hormone and an adrenergic neurohumor of the central and sympathetic nervous systems. In the brain and spinal cord, norepinephrine acts as a trans-synaptic mediator (Glowinski and Baldessarini, 1966) and as both an excitatory and inhibitory synaptic transmitter (Margules, 1968). Adrenergic nerve terminals, originating from cell bodies in the pons and medulla oblongata, extend in high concentration to the medial forebrain bundle (MFB), the hypothalamus, the reticular formation, the preoptic area, and the limbic system, with other collaterals extending to the cerebellum, the spinal cord, and to the entire cerebral cortex (Dahlstrom and Fuxe, 1965; Folkow and Neil, 1971; Fuxe, 1965; Fuxe, Hokfelt, and Jonsson, 1970; Hillarp, Fuxe, and Dahlstrom, 1966; Lichtensteiger and Langemann, 1966; Schildkraut and Kety, 1967; Stein and Wise, 1969; Vogt, 1954).

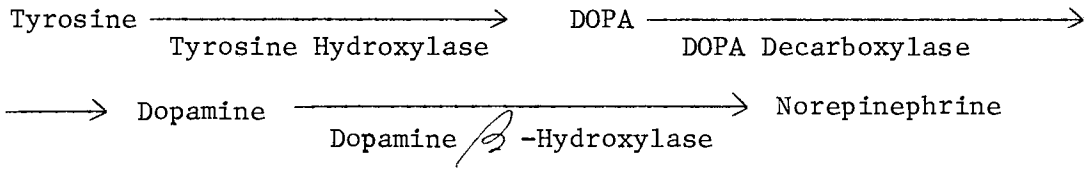
Noradrenergic neurons in the vasomotor center of the medulla oblongata within the brainstem reticular formation are active neural elements in an autoregulatory system for blood pressure control within the central nervous system (Folkow and Neil, 1971). In the body periphery, as an agent of sympathetic nervous activity and as a hormone released into the general circulation from the adrenal gland, norepinephrine has a pronounced influence upon total peripheral resistance and systemic blood pressure because it exerts a strong constrictive effect upon virtually the entire vasculature (Grollman, 1969). This effect is most marked on the vessels of the skin and kidneys and is less pronounced and more irregular on skeletal muscle blood vessels (Brod et al., 1969).

Norepinephrine and Emotion

The details of adrenergic morphology are signigicant not only when related to the chronic elevation of blood pressure, but also when related to the emotional behaviors that are more commonly associated with hypertension. The MFB, holding the largest concentration of ascending noradrenergic fibers in the diencephalon (Heller, Seiden, and Moore, 1966) is that part of the brain critical to so-called "hypothalmic-preoptic motivational mechanisms" (Roberts, 1970), mechanisms that largely control the behaviors of threat, attack, and mating. Other sites of adrenergic innervation, the preoptic area, the limbic system, and the hypothalamus are also subcortical structures associated with emotion and emotionally motivated behavior (Anden, Carlsson, and Haggendal, 1969; Bliss and Zwanziger, 1966; Flynn et al., 1970; Fuxe et al., 1970; Haggendal and Lindquist, 1964; Mowbray and Rodger, 1970; Olds, 1962; Olds

et al., 1964; Reis and Gunne, 1965; Stein and Wise, 1969; Wise and Stein, 1969).

Synthesis and Storage of Norepinephrine



Source: Costa, E. and N. H. Neff. 1966. Isotopic and non-isotopic measurements of the rate of catecholamine biosynthesis, p. 152. In E. Costa, L. J. Cote, and M. D. Yahr. (eds.) Biochemistry and pharmacology of the basal ganglia. Raven Press, New York.

Figure 1. Sketch Illustrating the Synthesis of the Catecholamine, Norepinephrine, from the α - Amino Acid, Tyrosine.

In spite of its wide distribution in the brain, norepinephrine is synthesized in relatively small quantities in brain tissue compared to the total metabolism of the amine in the body (Tepperman, 1968; Wurtman, 1965a; Wurtman, 1965b). Furthermore, brain tissue does not absorb norepinephrine from the general circulation since a blood-brain barrier to norepinephrine and to its metabolite, normetanephrine, is known to exist (Anden et al., 1969; Glowinski, Kopin, and Axelrod, 1965; Schildkraut, 1967; Uddin and Green, 1967). Tyrosine [2-Amino-3 (p-hydroxyphenyl) proprionic acid], the phenolic amino acid precursor of norepinephrine (Uddin and Green, 1967) does pass across the blood-brain barrier and is thought to do so by means of a specific transport mechanism rather than by passive diffusion (Chirigos, Greengard, and Udenfriend, 1960). Intraperitoneal injection of L-tyrosine in rats has shown that the amino acid as readily penetrates brain tissue as it does plasma and skeletal

muscle, although the site of transport into the brain has not been defined (Chirigos et al., 1960).

The neuronal storage granule within the postganglionic sympathetic neuron is the principal peripheral source of norepinephrine as a neurohumor in plasma, exceeding its output as a hormone from the adrenal gland (von Euler, 1956; Falck, 1962; Wurtman, 1965a; Wurtman, 1965b). Countless nerve fiber terminals containing clusters of such vesicles are present in nearly all body tissue (Wurtman, 1965a; Wurtman, 1965b) and are richly distributed in those organs of the body that are sympathetically innervated (Falck, 1962). These terminals are more sparcely distributed in the vasculature (Bhagat, 1971) and in the brain (Anden et al., 1966; Glowinski, 1970). As a hormone, norepinephrine is secreted from the chromaffin tissue of the adrenal medulla (Bhagat, 1971; Bolme et al., 1967a; von Euler, 1956; Falck, 1962; Fuxe, 1965: Fuxe and Hokfelt, 1970; Glowinski, 1970; Vogt, 1954).

By a process known as fractional turnover (Louis et al., 1969), norepinephrine is continuously released from vesicles into the cytoplasm of the nerve cell before it is released as a physiologically active neurotransmitter into the sympathetic neuroeffector junction (Uddin and Green, 1967; Wurtman, 1965a; Wurtman, 1965b). Berman and Siggins (1968) have postulated that Schwann cell-free terminal areas of postganglionic sympathetic vasoconstrictor fibrils are the sites of humoral release, and that these areas are located at discrete neuromuscular junctions in the walls of blood vessels. These sites have been further described as lying in the adventitial, or external layer and in the tunica media, or middle coat, the layer of the vessel wall that encloses the smooth

muscle fibers (Anderson and Brown, 1967; Brick, Hutchison, and Roddie, 1968; Brown, 1969; Burn, 1967; Burn, 1969; Falck, 1962).

Measurement of the specific activity of organ tissue catecholamines in mice has been performed by intravenous injection of radioactive tyrosine (L-tyrosine-H^3, DL-tyrosine-3-C^{14}), and radioactive DOPA (DL-dihydroxyphenylalanine-H^3), this last substance being a radioisotope of 3,4-dihydroxyphenylalanine, an intermediate in the catabolism of tyrosine and precursor of norepinephrine (Burack and Draskoczy, 1964). The procedure has identified the spleen, adrenal medulla, and particularly the liver and heart as significant sites of storage and synthesis (total turnover).

The rate of synthesis of norepinephrine from tyrosine is a negative function of the level of free, unbound, norepinephrine in the cytoplasm of the adrenergic and the chromaffin cell (Axelrod and Kopin, 1969; Costa and Neff, 1966). Norepinephrine is unbound when it has not yet been rendered physiologically inert following sympathetic nerve discharge and hormonal release. To be bound, norepinephrine must be taken up into the granulated vesicles within aminergic central and pre-synaptic sympathetic fiber terminals and into the adrenal medullary chromaffin cell (Goodall and Kirshner, 1958; Uddin and Green, 1967). Surface binding of the amine also occurs in collagenic tissue and in the basement membrane of all smooth muscle cells (Gillespie, 1968).

Two experiments (Burack and Draskoczy, 1964; Trendelenburg, 1961) have provided pharmacological evidence that norepinephrine may be retained in two pools within the individual granule in the postganglionic nerve ending. The first such pool is presumed to be small, functional, and a source of readily available norepinephrine during sympathetic innervation.

This storage site also seems susceptible to rapid depletion when the adrenergic nerve fiber is stimulated at frequencies that are supra-physiological (Folkow, Haggendal, and Lisander, 1967). The second pool is larger, non-functional, and only slowly transfers its contents to the functional pool. This model for the compartmentalized storage of norepinephrine in the nerve fiber was first conceptualized by Trendelenburg (1961) in a report on the dose-response curve to intravenous injection of the sympathomimetic drug, tyramine hydrochloride, in the spinal cat. In measuring blood pressure, heart rate, and the response of the nicitating membrane, he observed a "transmission fatigue" which he interpreted as resulting from reduction of "available", rather than "bound", norepinephrine. Burack and Draskoczy (1964) not only proposed two storage pools for norepinephrine, but also suggested that radioactive labeling of norepinephrine in nervous tissue may be nonhomogenous. They noted a differentiated rate of decline in specific activity of norepinephrine in the brain, heart, spleen, adrenal gland, and liver of mice after intravenous injection of radioactive tyrosine and radioactive DOPA. Trendelenburg (1964) argued that both conditions are indeed possible and his view has gained acceptance by other investigators (Folkow, Haggendal, and Lisander, 1967; Kopin, 1964; Sedvall, Weise, and Kopin, 1968; Weissman, Koe, and Tenen, 1966).

Monamine oxidase (MAO) is the enzyme that subjects norepinephrine to deamination when it is in the free state in the cytoplasm of the neuron (Uddin and Green, 1967). MAO is a mitochondrial isozyme (Fuller, 1972; Markert and Moller, 1959), meaning that it is either a protein of differing molecular forms, or that it is more than a single protein (Diaz Borges and D'Iorio, 1972; Youdim, 1972). The level of unbound

norepinephrine is determined both by the relative activity of MAO (Montcastle and Baldessarini, 1974), and by the availability of binding sites within the vesicles (Weise, Sedvall, and Kopin, 1967).

Binding of norepinephrine is generally considered to be the principal inactivating mechanism because the bound amine is neither susceptible to cytoplasmic deamination by MAO nor to O-methylation at the synapse by the enzyme, catechol-O-methyl-transferase (COMT) (Bhagat, 1971; Hertting and Axelrod, 1961; Louis et al., 1969; Panisset and Bourdois, 1968; Wurtman, 1965a; Wurtman, 1965b). This view of the binding mechanism does not, however, rest unchallenged. Studies of norepinephrine disposition in strips of rabbit thoracic aorta (Kalsner and Nickerson, 1969) have shown deamination and O-methylation to be more effective mechanisms of inactivation than vesicular binding. The finding may be explained by the discovery that binding in rabbit aortic strips takes place in the adventitia and underlying portion of the media of vascular smooth muscle, but that enzymatic breakdown of norepinephrine is the principal deactivating process in the greater part of the media (Levin and Furchgott, 1970).

Biosynthesis of norepinephrine can be increased when tissue is sympathetically stimulated (Anden, Fuxe, and Hokfelt, 1966; Weiner and Rabadjija, 1968). A relatively high rate of synthesis can also be a function of dense concentration in tissue of adrenergic nerve processes (Turner, 1966; Uddin and Green, 1967). When, for example, the stellate ganglia of the rat are electrically stimulated, the resultant increase in heart rate (90% above control levels) is accompanied by a pronounced (2-fold) increase in norepinephrine synthesis (Gordon et al., 1966). The systemic adrenergic influence of the heart is in fact so considerable

that it has been described as a neuroendocrine organ by Braunwald, Harrison, and Chidsey (1964). They found that mean arterial pressure and the contractile force of the right ventricle in the dog were significantly increased by the reinfusion of blood initially withdrawn from the coronary sinus following electrical stimulation of the cardiac sympathetic nerves. They found also that stimulation of the cardiac nerves in the dog produced a definite pressor effect following severance of the cardiac nerves from the rami and all central afferentations and administration of the beta (adrenergic) receptor blocking agent, Nethalide.

The Renin-Angiotensin System

Angiotensin II, an octapeptide, is an indirect product of the interaction between the proteolytic enzyme, renin, and angiotensinogen ($alpha_2$-globulin) which is a renin-substrate in plasma (Lubash, 1968; Pitts, 1968). Renin is released from the juxtaglomerular cells, the "intrarenal baroreceptors" in the afferent arterioles leading to the nephron of the kidney (Pitts, 1968). These granular cells respond to reduction in urinary sodium, to sympathetically induced partial renal anoxia, and to reduced renal perfusion pressure (Lubash, 1968). By reacting with angiotensinogen, renin liberates angiotensin I, the virtually inactive decapeptide precursor of angiotensin II (Pitts, 1968). Angiotensin II is an unstable and probably minute blood constituent under normal conditions (Zweifach, 1968), but it is, nonetheless, considered "by weight, the most powerful pressor substance known" (Lubash, 1968).

The renin-angiotensin system and the adrenal cortex form a negative feedback loop that modulates renal perfusion pressure, blood volume, and

the internal balance of sodium (Na), potassium (K), and water (Abboud, 1968; Gantt, 1967; Haber, 1969). Angiotensin II evidently inhibits the active transport, or resorption, of sodium into the renal tubules and of potassium into the adrenal cortex. These inhibitions disturb the extracellular Na/K ratio, causing sufficient imbalance to stimulate the secretion of the mineralocorticoid, aldosterone, from the zona glomerulosa cells of the adrenal cortex (Szalay, 1969). Aldosterone promotes the resorption of sodium into the renal tubules and the conservation of body water, adjustments that serve as inhibitory stimuli to the secretion of renin from the juxtaglomerular cells of the kidney (Lubash, 1968; Tanaka et al., 1969). A study of aldosterone pre-treated guinea-pigs has shown that aldosterone in fact fulfills antagonistic functions, at once promoting the pressor effects of angiotensin II and inhibiting the secretion of renin from the kidney (Beretta, Aguggini, and Rubbiani, 1967).

As a vasoconstrictor, angiotensin II has strong effect upon the vasculature of the kidney, moderate effect upon the blood vessels of the skin, and a sustained constrictor effect upon the vessels of striated muscle (Brod et al., 1969). The magnitude of these effects depends, in part, on the concentration of sodium at the receptor site (Blair-West, Harding, and McKenzie, 1968). The pressor function of angiotensin II does not seem to be centrally mediated. It has been injected into the vertebral and carotid arteries of the anesthetized dog in order to determine whether the maneuver might stimulate the vasomotor center (Zimmerman, 1967). Blood pressure elevation occurred only after the injection had caused constriction in the peripheral circulation and could not, therefore, be attributed to central stimulation.

The kidney has been found to exert an anti-hypertensive influence upon circulatory dynamics that plasma renin activity levels do not in themselves clearly reveal. Curiously, it moderates the cardiovascular response to the end-products of its own secretions, for the kidney is a storage site of angiotensinase, the enzyme that destroys angiotensin II (Pitts, 1968). It has been found, furthermore, that bilateral nephrectomy in the dog will produce an increase in mean arterial pressure (Bunag, McCubbin, and Page, 1968; Tigerstedt and Bergman, 1898). This animal preparation has also demonstrated pronounced elevations in blood pressure following infusions of both angiotensin II and renin (McCubbin and Page, 1954). The protective, compensatory role of the kidney has been demonstrated by the renal hypertrophy detected in rats following injection of either D-aldosterone of deoxycorticosterone trimethylacetate (DOCA) (Ostrovsky, Papsin, and Gornall, 1968). Hypertrophy developed before blood pressure became elevated. Furthermore, a phospholipid has been isolated from the kidney of the dog and the hog (Sen, Smeby, and Bumpus, 1967) and from the blood plasma and erythrocytes of the dog and the human (Ostrovsky et al., 1967) that will reduce blood pressure and indirectly inhibit renin activity in renal hypertensive rats (Smeby, Sen and Bumpus, 1967).

The Synergism between the Sympathetic Nervous System and the Renin-Angiotensin System

There are two kinds of evidence to demonstrate the synergism between norepinephrine and the renin-angiotensin system. Electrical stimulation of the mesencephalic pressor area (vasomotor center, bilateral portion) in the anesthetized dog elicits the release of renin from the

kidney (Ueda et al., 1967). Sympathetic fibers either innervate the juxtaglomerular cells directly or indirectly stimulate the release of renin and the consequent formation of angiotensin II by influencing hemodynamic shifts and the balance of electrolytes (Ueda et al., 1967).

Because angiontensin II is a weak depolarizing agent (Kiran and Khairallah, 1969), the converse may be true: by increasing the permeability of the cell membrane, angiotensin II probably augments the release of norepinephrine from the adrenergic neuron (Boadle, Hughes, and Roth, 1969; Day and Owen, 1968a; Day and Owen 1968b; Day and Owen, 1969; Dickinson, de Swiet, and De Schaepdryver, 1968; Kiran and Khairallah, 1969; Panisset and Bourdois, 1968; Peach and Ford, 1968; Turker and Kayaalp, 1967; Zimmerman, 1967). It is this biochemical property that may explain why angiotensin II infusion has been found to raise blood pressure and to produce a non-rhythmical efferent activity in the renal sympathetic nerve of the rabbit (Aars and Akre, 1968). This property may also explain the indirect stimulation of sympathetic ganglia (Lewis and Reit, 1965; Trendelenburg, 1966), the facilitation of ganglionic transmission (Haefely, Hurlimann, and Thoenen, 1966), and the direct stimulation of catecholamine secretion from the adrenal medulla (Lubash, 1968; Tanaka et al., 1969) by angiotensin II.

Renal-Adrenocortical Function in Essential Hypertension

The anomoly in renal-adrenocortical function in hypertension may have to do with the relative activity levels of the enzyme, renin, and the salt-retaining hormone, aldosterone. Renin values have been found to be either normal or below normal in essential hypertension (Del

Greco et al., 1967; Haber, 1969; Januszewicz, Baczko, and Wocial, 1969; Lubash, 1968; Matsuyama et al., 1967; Schonbeck et al., 1969). When neurogenic hypertension has been produced in rats by sinoaortic baroceptor denervation, renin values have remained unchanged (Matsuyama et al., 1967). When human subjects with essential hypertension have undergone the salivary Na/K ratio test (an index of mineralocorticoid excess), plasma renin activity has been found to be suppressed and to be accompanied by an increase in the concentration and activity level of aldosterone (Adlin, Channick, and Marks, 1969). Therefore, although the pressor effect of angiotensin can be somewhat offset by the hypotensive properties of the kidney, low plasma renin activity in essential hypertension will augment the salt-retaining capacity of aldosterone. This possibility is reasonable when it is recalled that the actions of angiotensin II and aldosterone are antagonistic and that angiotensin II is an indirect by-product of renin activity.

Noradrenergic Processes in Essential Hypertension

The abnormality in the adrenergic process in essential hypertension has been presumed to be in the binding of norepinephrine. If granular storage capacity and sympathetic nervous activity can be assumed to be inversely related, decreased granular retention of norepinephrine must result in elevations of free norepinephrine in the cytoplasm of the chromaffin cell and aminergic neuron, in the bloodstream, and at the neuroeffector junction in smooth muscle. High blood pressure might then be expected to ensue from the generalized vasoconstriction which these elevations bring about (de Champlain, Krakoff, and Axelrod, 1967; de Champlain, Krakoff, and Axelrod, 1968; DeQuattro and Sjoerdsma, 1968;

Gitlow et al., 1969; Kopin, 1964; Krakoff, de Champlain, and Axelrod, 1967; Mendlowitz et al., 1961; Nestle and Doyle, 1968). One group of investigators (Louis et al., 1969) has, however, pointed out that these deductions are not entirely logical since defective binding necessarily exposes more norepinephrine to deamination by MAO.

It is instead conceivable that some sort of intraneuronal autoregulation may occur during states of adrenergic activation, - that there exists a compensatory mechanism by which norepinephrine is metabolically conserved, its concentration adjusted to the needs of the cell (Costa and Neff, 1966; Weise et al., 1967). Four separate studies not only suggest the possiblity of such a mechanism, but also illustrate some of the psychological and cardiovascular correlates of adrenergic activation.

Goldberg and Salama (1969) found high norepinephrine content in the forebrain of rats following the muricidal (mouse-killing) response (25.5% increase) notwithstanding their pre-treatment with an inhibitor of norepinephrine synthesis, the tyrosine hydroxylase inhibitor, L-alpha-methyl-para-L-tyronsine (α-MPT). Brain norepinephrine levels have been seen to increase in male mice made aggressive by isolation and subjected to short, daily episodes of fighting and to being witness to fighting (Welch and Welch, 1971). These animals also developed high blood pressure and distinct cardiac hypertrophy within as short a time period as 10 days. High levels of norepinephrine have been found in the forebrain and cerebellum of spontaneously hypertensive rats (SHR) (Robertson et al., 1968). Lastly, muricidal and rod-gnawing responses in pre-isolated SHR at varying ages (4.5, 19, and 42 weeks) have been found to

be considerably more aggressive than these same behaviors in control rats (Shimamoto and Nagaoka, 1972).

SHR, it should be explained, is considered one of the more appropriate experimental models of human essential hypertension (Knudsen, Iwai, and Dahl, 1973). In both this animal and in man, hypertension develops with age, and can be spontaneously elicited by environmental stimuli (Grollman, 1972). In SHR, it has been produced by forced immobilization (stress loading) and by mild, continuous forms of visual, auditory, or electrical stimulation (Grollman, 1972; Okamoto and Oaki, 1963; Okamoto, 1969; Phelan, Eryetishir, and Smirk, 1962; Smirk and Hall, 1968). As in man (McKusick, 1960), hypertension in SHR is polygenetically determined and regulated by a relatively small number of major genes (Hansen, 1972; Okamoto, 1969; Phelan et al., 1972; Tanase et al., 1972). Whereas organic malfunction or abnormality does not initiate hypertension in either man or SHR, both organisms are prone to cardiac hypertrophy and to hypertrophic and lesional pathology of the arteriolar network as the disease progresses (Folkow et al., 1972; Grollman, 1972; Phelan et al., 1972).

In the Welch and Welch study (1971), post-mortem analysis of brain tissue disclosed increased amine levels in the telencephalon and diencephalon-mesancephalon, the areas of the brain that contain noraminergic nerve terminals. Decreased levels were noted in the pons and medulla oblongata, the sites of the cell bodies. The discrepancy seemed to indicate that axoplasmic flow carrying neurotransmitter from cell body to nerve terminus (Dahlstrom and Haggendal, 1966; Kapeller and Mayor, 1967; Laduron and Belpaire, 1968) can be accelerated by stimulation and that reduction of brain tissue oxygen tension (pO_2) may inhibit the

activity of MAO. The latter assumption evolved from a series of deductions made by Welch and Welch (1971) to defend the hypothesis of an intraneuronal autoregulatory process governing the metabolism of norepinephrine. According to this view, norepinephrine is conserved under precisely those conditions of arousal in which it is most needed.

These authors began with the implicit premise that oxygen utilization in all body tissue is made possible by a respiratory chain of enzymes. This is a group of proteins, cytochromes, and nucleotides that are constituents of mitochondria (Chance, 1957). The isozyme, MAO, is part of the chain. It is an oxygenase, an enzyme that catalyzes the direct incorporation of the entire oxygen molecule into substrate (Mahler and Cordes, 1966). Regardless, therefore, of either substrate, tissue, or species, MAO is extremely sensitive to tissue reserves of dissolved oxygen, namely pO_2 (Davies and Bronk, 1957; Novick, 1966).

Taking this property of MAO into account, Welch and Welch derived their second premise from oxygen cathode implantation studies of the cortical surfaces of the lightly anesthetized cat (Davies and Bronk, 1957) and the normal conscious cat (Clark and Misrahy, 1957). Both studies reported spontaneous, rhythmic fluctuations in cortical pO_2 resulting from alternating vasodilatation and vasoconstriction. These fluctuations indicated that normal cortical pO_2 levels were so low as to be marginal, never far from anoxia. This "disconcerting" discovery emerged, of course, from only localized investigation of the cortex (Davies and Bronk, 1957). Welch and Welch nevertheless generalized from this finding to contend that stress that is specific to defensive, aggressive behavior may bring about widespread reduction of pO_2 within the central nervous system. They noted, further, that osmotic change

within the neuron during nervous excitement has been thought to cause either mitochondrial shrinkage or swelling (Lehninger, 1967), and that these structural modifications have been shown to lessen O_2 consumption by mitochondria (Aebi, 1962).

Within its limits, this argument may be plausible, but it does not take into account the effect of low pO_2 upon the rate-limiting step in the synthesis of norepinephrine. This step is the conversion of tyrosine to DOPA by the primary catalyst in the conversion process, tyrosine hydroxylase (Levitt et al., 1965; Nagatsu, Levitt, and Udenfriend, 1964). The sensitivity of tyrosine hydroxylase to pO_2 has been ascertained by studying its activity in high O_2 atmosphere, both _in vitro_ and _in vivo_. At a normal O_2 atmosphere of 20 per cent, which creates an atmospheric pressure of approximately 159 mm. Hg, - normal tissue pO_2 being somewhat less than 70 mm. Hg (Neff and Costa, 1967) - oxygen has been found to virtually saturate the enzyme _in vitro_ (Ikeda et al., 1966). Reflecting this phenomena, catecholamine synthesis rate in heart and brain has been found to nearly double in rats subjected to an O_2 atmosphere of 100 per cent for a 1 hour period (Neff and Costa, 1967). MAO activity also presumably increased during this same time period.

So it would seem that there are at least two explanations for the findings of the Welch and Welch experiment. First, aggressive behavior might indeed reduce pO_2 and by so doing, lessen the efficacy of mitochondria, of MAO, and of tyrosine hydroxylase. In this event, norepinephrine would be protected from deamination even as its synthesis may be reduced. Conversely, aggressive behavior may increase pO_2. Such an increase should accelerate and counterbalance the activity of both enzymes, but it should finally favor the initial catalyst in nore-

pinephrine biosynthesis. In view of the nervous, hormonal, and myogenic processes that are known to come into play in the defense response, this second explanation seems closer to the facts. It also seems to be more biologically sound.

Summary and Conclusions

The hypertensive response has been described in terms of adrenergic processes within the brain and autonomic nervous system in terms of vasoconstriction of the intestines, kidneys, and skin, in terms of circulation in skeletal muscle and, finally, in terms of cardiac activity. Of the internal secretions that directly influence the peripheral circulation, (acetylcholine, epinephrine, norepinephrine, and angiotensin II), the latter two not only appear to have the more acute and pervasive effect upon total peripheral resistance, but seem also to be synergistic in their effects on the renal pressor and sympathetic nervous systems. It is likely that the pressor effect of angiotensin II is somewhat offset by the normal hypotensive properties of the kidney. It may also be offset by low plasma renin activity, occasionally symptomatic of essential hypertension, that can augument the salt-retaining capacity of aldosterone.

Although it is possible in hypertension that norepinephrine is not properly bound within the neuronal storage vesicle, there are two other plausible explanations for the heightened sympathetic nervous activity that is symptomatic of the disease. Stimulus-dependent suppression of the deaminating isozyme, MAO, may take place and increase the concentration of norepinephrine within the axon of the neuron; or, it is possible that stimulus-dependent acceleration of noradrenergic metabolism produces a substantial functional reserve of neurotransmitter.

CHAPTER III

THE BAROCEPTORS AND THE CONTROL OF SYSTEMIC BLOOD PRESSURE

Sensitivity of the carotid sinus/aortic arch inhibitory reflex to blood pressure elevation has made it an important area of research on essential hypertension. The baroceptors of the carotid sinus and aortic arch, the vasomotor center in the reticular formation of the lower brainstem, the heart, and the peripheral arterial vessels are together considered an afferent-efferent reflex arc and a servocontrol system for systemic arterial pressure (Rosenbaum and Race, 1968).

The Structure and Function of the Carotid Sinus/Aortic Arch Reflex

Baroceptors have terminal end-plates that are attached to the adventitia and tunica media of the arch of the aorta and the internal carotid arteries (Abraham, 1969). These receptors are sensitive to mean intrasinusal pressure, to rate of change in arterial pressure, and to stretch or distortion of the arterial wall (Dell, 1972; Greenfield and Tindall, 1968; Heymans, 1968). The vagus and the glossopharyngeal nerves are the two afferent pathways from the sensor sites to the medial inhibitory portion of the bulbar vasomotor center, the center of the brain that continuously regulates vascular tone (Biscoe and Purves, 1967; Bronk et al., 1936; Gernandt, Liljestrand, and Zotterman, 1946;

Haddy, Overbeck, and Daugherty, 1968; Miura and Reis, 1968; Sampson and Biscoe, 1968). Potentials evoked by direct electrical stimulation of the carotid sinus nerve and recorded in the commissural nucleus of Cajal, the nucleus of the solitary tract, and in various areas of the reticular formation in the anesthetized cat, have indicated that afferent fibers of the sinus nerve make monosynaptic connections with the vasomotor center (Humphrey, 1966; Miura and Reis, 1968; Sampson and Biscoe, 1968).

These various structures perform the critical function of maintaining a predominantly steady non-pulsatile blood flow to the brain through the internal carotid arteries at normal ranges of blood pressure (Dell, 1972; Greenfield and Tindall, 1968; Heymans, 1968). Because the inhibitory reflex is frequency-dependent, it is set in motion by pulsatile intrasinusal pressure brought about by rise in blood pressure and increase in heart rate; this pulsatile pressure inhibits sympathetic discharge by initiating volleys of baroceptor impulses which travel along the nucleus of the solitary tract to the medial, vagal portion of the vasomotor center (Abrahams et al., 1964; Dell, 1972; Gero and Gerova, 1962; Green and Heffron, 1968).

The bilateral portion of the vasomotor center is tonically active, continuously transmitting impulses through adrenergic vasoconstrictor nerve fibers to all the peripheral blood vessels excepting the capillaries (Delius et al., 1972; Grollman, 1969; Guyton, 1966; Hagbarth and Vallbo, 1968). Adrenergic innervation is responsible for vasomotor tone, a slight, constant constriction of the peripheral blood vessels (Bolme et al., 1967a; Cobbold et al., 1963; Hadjiminas and Oberg, 1968). Tonus of the larger arterial blood vessels of the body is also partly

accounted for by basal adrenal medullary secretion of norepinephrine (Guyton, 1966; Zweifach, 1968). In contrast, cholinergic vasodilatory fibers are not influenced by the baroreflex (Uvnas, 1960a). There is no intrinsic tonicity, therefore, to their innervation of blood vessels.

The influence of the vasomotor control center upon basal vascular tone is predominant in the arterial vessels of skeletal muscle (Barcroft, 1968). These vessels receive more vasomotor stimulation and are more involved in the baroreflex arc than are either the veins (Folkow, 1962b; Hadjiminas and Oberg, 1968), the renal and skin circulation, or the vascular bed of the intestine (Hadjiminas and Oberg, 1968; Lofving, 1961a; Lofving, 1961b). These regional discrepancies may result from selective negative feedback; that is, elevation in the controlled variable (central blood pressure) stimulates baroceptor reflex inhibition of only certain peripheral vasoconstrictor fibers (Lofving, 1961a; Lofving, 1961b). Because the blood vessels in skeletal muscle constitute approximately half of the entire circulatory system (Guyton, 1966), it is not surprising that the reactivity of these vessels is considered an important regulatory element in circulatory homeostasis (Heymans and Neil, 1958; Peterson, 1963; Scher and Young, 1963).

Control of Peripheral Resistance

Peripheral resistance in general, and the pressor response in particular, are indirectly mediated by vasomotor fibers from the motor and premotor cortex, the orbital area of the forebrain, the rostral cingulate gyrus, the postero-lateral hypothalamus, and the anterior temporal lobe, all of which stimulate the vasomotor center (Guyton, 1966; Lofving, 1961a). The principal site of peripheral resistance in

all body tissue is the arteriole (Cobbold et al., 1963; Freis, 1960; Rodda and Denny-Brow, 1966) and it is the only segment of the circulation that is innervated by both constrictor and dilatory vaomotor fibers (Bolme et al., 1967a).

Characteristics of Smooth Muscle Cell Response

The smooth muscle cell in the arterial microcirculation is considered at once a receptor and an effector unit (Golenhofen, 1968; Penaz, Burianek, and Semrad, 1968). As a receptor cell, the smooth muscle cell responds to vasomotor activation (Barcroft, 1968; Golenhofen, 1968); as a stretch receptor (Penaz et al., 1968), it also responds to the two autonomous, local influences of perfusion pressure and the metabolic processes of blood-tissue exchange (Haddy et al., 1968; Penaz et al., 1968; Thron, 1968; Zweifach, 1968). The attendant effector response within the cell is presumed to be a mechanical reflex of negative feedback which controls the diameter of the blood vessel (Delius et al., 1972; Penaz et al., 1968). The delay, or phase lag, between the cellular receptor and effector responses produces oscillation, or resonance, in the internal muscle layer of the arteriole (Folkow, 1964a; Flokow, 1964b; Johnson, 1964; Penaz et al., 1968; Thron, 1968). It is believed that efferent impulses from the smooth muscle cells in the arterioles contribute their part to the reflex arc governing systemic blood pressure (Rosenbaum and Race, 1968).

Noradrenergic Innervation of the Carotid Arterial Structures

An abundance of cervical sympathetic fibers innervate the branching

of the carotid sinus and the internal carotid artery (Reis and Fuxe, 1968). Synapses exist between the carotid sinus nerve endings (vagal and glossopharyngeal) and sympathetic fibers (Koizumi and Sato, 1969), and norepinephrine stores appear to be released within the walls of the carotid sinus and the carotid artery by electrical stimulation of the cervical sympathetic nerve (Reis and Fuxe, 1968). Nonetheless, norepinephrine apparently neither influences the distensibility of the internal carotid artery in man (Abraham, 1969; Arndt, Klauske, and Mersch, 1968), nor in the favored experimental model of essential hypertension in man, the spontaneously hypertensive rat (SHR). Intravenous and intracarotid administration of norepinephrine does not reduce internal carotid arterial blood flow in humans (Greenfield and Tindall, 1968), and although carotid occlusion in the dog and simulated hemorhage in man (induced by lower body suction) each activate the reflex in response to fall in arterial pressure, neither maneuver produces significant increase in catecholamine secretion (Hodge, Lowe, and Vane, 1969).

Carotid Sinus/Aortic Arch Inhibitory Reflex Function in Hypertension

In essential hypertension, it has been thought that the baroceptors cease to function after becoming sensitized and finally exhausted by persistent high blood pressure (Abraham, 1969). This circumstance has been understood to produce a "resetting" of the protective reflex of negative feedback at higher levels of systolic pressure (Freis, 1960; Peterson, 1961).

If local adrenergic influence upon the carotid sinus stretch reflex

must be discounted as a direct contributing factor to the resetting of threshold, reduction in arterial compliance from medial hypertrophy is indeed believed to influence threshold (Bristow et al., 1969). There is now sufficient evidence from the study of hypertensive animal and human subjects to suggest that resetting of baroceptor threshold is a function of hypertrophically induced incompliance at the site of the receptors. In other words, it is the arterial walls, rather than the receptors, that may have become reset (Folkow et al., 1972). For example, studies of renal hypertensive rabbits (Aars, 1969a; Aars, 1969b) have shown that resetting of the reflex occurred after thickening of aortic tissue had taken place in the area of the baroceptors. Modification of the vessel wall mass took place within a week in some animals.

Hypertrophy has been described as a rebuilding, rather than a sclerotic narrowing, of the vessel wall (Folkow et al., 1970a; Folkow et al., 1970b). It is viewed as a form of vascular adaptation whereby resistance to blood flow rises throughout the arterial system in proportion to intermittent or prolonged elevation of blood pressure (Pickering, 1968; Sivertsson, 1970). Hypertrophy of the vessel media inside the smooth muscle sheath increases the wall/lumen ratio which then encroaches upon the lumen (the vessel bore) in proportion to average pressure load (Folkow et al., 1972; Sivertsson, 1970; Suwa and Takahashi, 1971). Furthermore, venous occlusion plethysmography on human subjects with essential hypertension has shown that resistance in the hand and forearm persists and may increase at maximal vasodilatation (Conway, 1963; Folkow, 1956; Folkow, Grimby, and Thulesius, 1958; Sivertsson, 1970; Sivertsson and Olander, 1968). These experiments have utilized high, indirect plethysmograph temperature (33^{o}-43^{o}C) in order to minimize

sympathetic vasoconstrictor fiber discharge in the limb under study.

Similar results have been obtained in SHR in studies of flow resistance in both the isolated limb and in the entire systemic circulation (Folkow et al., 1970b). Resistance to blood flow following maximal vasodilatation was found following Nembutal anesthesia (3 mg./100 g. body weight), arterial perfusion of the isolated hindquarter (constant flow with oxygenated plasma substitute), and injections of the vasodilator, papaverine (a benzylisoquinoline alkaloid of opium). Blood flow resistance in SHR was found to increase in approximate proportion to blood pressure level under resting conditions when the sympathetic nervous system was blocked by guanathidine (0.51 mg./100 g. body weight), the root of the aorta perfused with an oxygenated plasma substitute, and the systemic circulation (excepting the coronary arteries) maximally dilated by intravenous injection of isopropylnoradrenaline and acetylcholine (Folkow et al., 1970a).

Hypertrophy of the arterial vessels apparently coexists with normal basal tone; that is, with normal smooth muscle activity (Conway, 1963; Pickering, 1936; Prinzmetal and Wilson, 1936; Sivertsson, 1970). Although associated with a normal range of resistance adjustments (vasodilatation and vasoconstriction) (Sivertsson, 1970), hypertrophic alteration of the arterial walls has the overall effect of raising the baseline for these adjustments (Folkow et al., 1970a; Sivertsson, 1970).

Flow resistance in the blood vessel is profoundly affected by hypertrophy since resistance has been described as being inversely proportional to the fourth power of the vessel radius (Sivertsson, 1970). Finally, hypertrophy is associated with increased reactivity to norepinephrine. Graded norepinephrine infusion to the hand in the hyper-

tensive subject administered through the ipsilateral brachial artery at dosages above threshold has produced markedly greater increase in flow resistance than that observed in the control subject (Sivertsson and Olander, 1968). The response indicates a more extreme attrition of the lumina for a given degree of smooth muscle contraction, and therefore represents a kind of enhanced vascular reactivity (Sivertsson and Olander, 1968).

Influence of the Central Nervous System upon Baroceptor Function

Aside from morphological change at the site of the baroceptors, servo-control of blood pressure in the reflex arc may be "over-ridden" in hypertension by higher centers of the brain (Folkow, 1962a; Manning, 1965). Anatomical and functional links between hypothalamic nuclei and the carotid sinus baroceptors have been demonstrated. Applying static pressure pulses to these receptors, Hilton and Spyer (1969) recorded both activation and inhibition of neurons within the anterior hypothalamic depressor area. Vagal activity, which normally lowers blood pressure, can be inhibited by hypothalamic stimulation: electrical stimulation of the lateral and posterior hypothalamus in both anesthetized and artificially respired unanesthetized cats can induce hypertension, excitation of the bilateral portion of the vasomotor center, and inhibition of the efferent cardiac vagal impulses which form part of the baroceptor response (Gebber and Snyder, 1970; Hilton, 1965).

Summary and Conclusions

The baroceptors are the primary sensors of a fairly complicated

system for blood pressure control. They are monitors of heart rate and of intrasinusal and aortic pressure, and ensure proper blood supply to the brain. In addition, the direct nervous connection of the baroceptors to the vasomotor center involves them in the maintenance of vasomotor tone in all segments of the peripheral circulation with the exception of the capillaries.

If a disturbance in the carotid sinus/aortic arch reflex exists in essential hypertension, it probably resides in these receptors and in the arterial media that surrounds them. For it is thought that the protective function of the baroceptors can be overwhelmed by neural bombardment of the bilateral vasomotor center from the hypothalamus during emotional arousal, and that their threshold of response can either become elevated or their sensitivity destroyed by sinusal and aortic hypertrophy.

CHAPTER IV

CIRCULATION IN SKELETAL MUSCLE

The Relationship Between Musculoskeletal Behavior and Circulation in Muscle

Hemodynamics and Metabolism in Normally Functioning Muscle

Skeletal muscle blood vessels are known to react as sensitively to central and sympathetic stimulation as does the visceral circulation. Circulation in skeletal muscle is controlled by the same cortical and diencephalic centers that alter blood flow to the internal organs, and by those same receptor-effector areas of the pons and medulla oblongata that reflexively adjust blood flow to both the viscera and the brain (Hilton, 1968; Hudlicka, 1968). Skeletal muscle blood flow is controlled predominantly by sympathetic cholinergic vasodilatory fibers that originate from the upper and midbrain (Eliasson et al., 1951; Golenhofen, 1968; Uvnas, 1960a; Uvnas, 1960b). It will be recalled that vascular tone in skeletal muscle is adrenergically mediated and is under the direct control of the vasomotor center of the brainstem (Barcroft, 1968). Blood supply to muscle is therefore continuously influenced by two neurologic systems. It has also been noted that the bilateral, excitatory portion of the vasomotor center can be stimulated by vasomotor fibers originating in the motor brain and hypothalamus, and that

this stimulation can override the vagal, inhibitory influence of the medial vasomotor center (Delius et al., 1972; Gebber and Snyder, 1970; Hagbarth and Vallbo, 1968; Hilton, 1965; Lofving, 1961a).

Full contraction and relaxation of muscle in exercise permits the uptake of oxygen and glucose, the acceleration of muscle metabolic rate, and the clearance of sodium and iodine from muscle tissue (Brod, 1962; Hyman et al., 1959; Renkin, 1968; Rosell and Uvnas, 1962). These processes together bring about what is known as the "breakthrough" of metabolites (Folkow, 1964a). It is the flow of blood and blood-borne constituents between the distal end of the arterial tree (the arterioles, the metarterioles, the precapillary sphincters, and the capillaries) and the tissue cell (Freis, 1960; Freis, 1969; Imbriglia, 1959; Sommers, 1959). The breakthrough counteracts and finally negates the initial adrenergic effect of vasoconstrictor fibers upon muscle vessels (Folkow, 1964a; Kjellmer, 1965). Metabolites are, in fact, powerful dilator substances that can quickly reinstate optimal diffusion capacity in the microcirculation during lumbar sympathetic (adrenergic) chain stimulation even as the larger, more distal vessels remain constricted (Folkow, Sonnenschein, and Wright, 1968).

Sympathetic cholinergic vasodilator fibers also dilate the blood vessels of skeletal muscle in exercise (Roddie, 1966; Uvnas, 1960a). Muscular contraction itself, however, and the motor innervation originating in the motor and premotor cortices of the precentral gyrus, are the most important mediators of peripheral vasodilation (Barcroft, 1968; Hilton, 1968; Hudlicka, 1968; Zanchetti, 1970). In response to strenuous exercise, blood flow in skeletal muscle in normal humans can increase from 1 to approximately 20 liters per minute (Barcroft, 1968),

reflecting the shift of blood from the skin, the kidneys, and the splanchnic area to skeletal muscle (Brod, 1962). Under these conditions, cardiac output increases from 5 to approximately 25 liters per minute and blood pressure remains essentially the same (Barcroft, 1968). Adams et al. (1969) measured circulatory response in the aorta, the mesenteric artery, and the external iliac artery in the cat during fighting behavior. After an initial moderate rise, blood pressure returned to normal resting level and remained at that level throughout the fighting episode. In a complementary study, Baccelli et al. (1968) found that when the hindlimbs supported the cat in combat, vasodilatation occurred in the iliac bed after an initial vasoconstriction, indicating that vasodilatation fulfills a metabolic function under local regulation. However, when the animal fought while lying on its side, iliac vasoconstriction took place, accompanied by a moderate but sustained rise in blood pressure.

Gross Skeletal Muscle Behavior in the Hypertensive Organism

Even though response in muscle circulation to restraint or immobilization has been largely the subject of animal, rather than human, research and although there is no disease in any experimental animal that is exactly comparable to essential hypertension in man (Gitlow et al., 1969), extrapolations can be made from animal research to the possible role of muscular rigidity in the pathology of essential hypertension since this rigidity may be a distinguishing somatic trait in the disease.

In essential hypertension, an asynchrony may exist between the

muscular and circulatory adjustments which ready an individual for an aggressive act and the motor inhibition of that act, an inhibition that cannot prevent the continued mobilization and tensing of muscle (Diamond, Balvin, and Diamond, 1963; Shmavonian et al., 1968). In keeping with this hypothesis, the observation has been made that the hypertensive person displays a state of muscular preparedness (Brod, 1962) as if "mobilized for combat" (Wolf et al., 1955). He may thus be demonstrating what Graham (1972) has called "the correlation of non-language behavior with disease."

Studies of hypertensive animals also report idiosyncrasies in gross muscular behavior. Griew (1966) noted less spontaneous activity in young SHR than in control rats in swimming behavior and in the Open Field situation. Welner et al. (1968) reported constrained behavior in young, pre-hypertensive "sensitive" rats in a cage setting designed for exploration. Cornary arteriosclerosis has been found in swine isolated from the age of 6 to 15 months (Ratcliffe et al., 1969), and the separated animals also displayed withdrawal behavior by their unwillingness to move about their cages and by their refusal to eat. Other swine, subjected to crowding over the same period of time, did not develop sclerotic lesions. It was therefore concluded that a disturbance in behavior pattern may have been a cause of disease.

Metabolic Disturbances in Muscle

Anoxia in Body Tissue

Hypertension in humans, like "muscle degeneration disease" in swine (Briskey, 1964), has been classified as one of the anoxic diseases (Hicks and Warren, 1950). The two areas of the human body to which this

generalization applies most appropriately are the kidneys and the skeletal muscles. Noradrenergic sympathetic influence upon either the renal artery or the afferent renal glomerular arterioles can cause partial anoxia as well as ischemia in the kidney (Lubash, 1968; Pfeiffer and Wolff, 1950; Pitts, 1968; Sommers, 1959). High sustained peripheral resistance can produce anoxia in skeletal muscle by bringing about degenerative changes in the elastic fibers of the arterioles that will interfere with efficient capillary blood-tissue interchange (Freis, 1960; Freis, 1969; Imbriglia, 1959). Degrees of anoxia can also be present in skeletal tissue in those states of emotional arousal in which anticipatory cardiovascular response and muscular immobility concur; therefore, it is believed that bodily restraint, whether imposed upon an organism, or deliberately self-imposed, can influence muscle metabolism in a significantly different way than does exercise (Brod, 1962; Charvat et al., 1964).

Muscle Pathology in Swine

Of all animal species, it is the pig that is regarded as the more appropriate subject for the investigation of homeostatic reflex mechanisms and cardiovascular function as these processes occur in man (Pekas and Bustad, 1965; Rowsell, 1968; Schmitt, 1968). Muscle degeneration disease in swine also seems to offer an adequate illustration of how strongly circulation in striated muscle may affect these processes in hypertensive man.

The disease is a pathological reaction in skeletal muscle to such stressors as fatigue, emotional excitement, noise, anoxia, high temperatures, and bodily restraint (Briskey, 1964; Briskey, 1969; Forrest

et al., 1968; Judge, Briskey, and Meyer, 1966). Degenerative lesions have been a consistent finding in post-mortem analysis of samples of longissimus dorsi muscle in stress-susceptible swine (Poland China, heat-stressor-susceptible) following immobilization stress (Judge, Cassens, and Briskey, 1967; Judge et al., 1967). The muscle tissue has been found to be in a condition of myomalacia, being typically soft, pale, and exudative in contrast to the firm, well-pigmented muscle tissue of normal swine at time of exsanguination (Briskey, 1964; Forrest et al., 1968). Judging from the relatively rapid rate of rigor mortis, the breakdown of carbohydrates had probably proceeded under relatively anaerobic conditions in the living animal (Henrickson, personal communication; Judge, Cassens, and Briskey, 1967).

Vascular Pathology in Skeletal Muscle and Viscera in the Human

In essential hypertension, degeneration of the arteriolar network in skeletal muscle and in the body organs are evidently identical. The salient feature of this degeneration in all body tissue has been described as "a diffuse lesion of the arteriolar bed" (Imbriglia, 1959). It is the result of a pathologic progression of hypertrophy, fibrosis, and necrosis (Freis, 1960; Freis, 1969; Imbriglia, 1959; Sommers, 1959). These structural changes reflect a depression in the metabolism of the smooth muscle cell brought about by anoxia (Robinson, 1960; Tobian, 1960). The level of the nucleotide, adenosine triphosphate (ATP), in the nucleoplasm and cytoplasm of the cell is lowered because the level of ingredients necessary to its reconstitution in the mitochondria, such as adenosine diphosphate (ADP) and oxidized cellular nutrients (fats,

proteins, and carbohydrates), is itself lowered (Guyton, 1966; Robinson, 1960; Tobian, 1960). Loss of ATP has serious consequences. The processes of oxidative phosphorylation and of active transport across the cell membrane are impeded, and relaxation of muscle fiber in the blood vessel wall is inhibited (Guyton, 1966; Robinson, 1960; Tobian, 1960). The loss also disturbs intracellular-extracellular ionic balance (Na/K ratio) by tending to reverse the normal concentration gradient of these ions (Guyton, 1966). Deprived of the energy of ATP, the sodium pump cannot prevent swelling of the smooth muscle cell brought about by the entry of sodium into the cell and the diffusion of potassium into the extracellular fluid (Guyton, 1966; Robinson, 1960; Tobian, 1960; Solomon, 1962).

Summary and Conclusions

Musculoskeletal behavior in both man and animal can evidently have significant effects upon cardiovascular homeostasis and upon the condition of skeletal muscle tissue itself. Full discharge of muscular tension following mobilization of whole body musculature allows blood pressure to return to normal levels after the initial elevation that normally accompanies sympathetic arousal. By initiating dilatation of muscle blood vessels, full discharge also permits optimum passage of nutriments and wastes to and from muscle tissue.

There seems sufficient evidence from observations of hypertensive man, of the spontaneously hypertensive rat, and of swine afflicted with coronary heart disease, to presume that some relationship must exist between constrained motor behavior and the autonomic, visceral component in cardiovascular disease. The relationship is perhaps best illustrated

at the site of the arteriole in both muscle and viscus. Here it has been seen that sympathetic activation and muscular constraint, or immobilization, may be sufficiently antithetic in their circulatory effects to produce anoxia and an anaerobic metabolic chain reaction that can be undermining to the entire microcirculation of the body.

CHAPTER V

THE PSYCHOPHYSIOLOGY OF ESSENTIAL HYPERTENSION

The Relationship between Physiological Response Patterns and Personality in Essential Hypertension

It may be true, as Pribram (1967) has stated, that sensory, hormonal, and neurosecretory receptor-effector processes in the central nervous system and between the central nervous system and the target organs of the body form the physiological substrate of mood. Mood is probably as Nauta (1963) has described it, "the attitude of the organism toward its outer and inner environments". In the context of opinions such as these, it seems reasonable to consider three questions. (1) Can the psychological correlates of noradrenergic activation and the hypertensive pressor response be translated into long-term psychological statements (Graham, 1972) to describe personality in essential hypertension in terms of specificity-of-attitude? (2) Are these psychological statements sufficiently specific to hypertension that they do not risk being applicable to other functional disorders as well? And (3) can specificity-of-attitude be correlated with certain kinds of individual autonomic response specificity in essential hypertension such as pressor hyperreactivity, and the "anger-out", norepinephrine-epinephrine response?

Specificity-of-Attitude in Essential Hypertension

After many years of research by many different investigators, descriptions of the hypertensive personality have evolved a common core. Competitiveness and compulsive drive apparently coexist with feelings of inadequacy that are sufficient to inhibit self assertion. These incompatible needs produce frustration and conflict that are both internally and externally directed, as first one, and then the other, of the individual's major drives gains ascendency (Ackerman, 1950; Alexander, 1948; Alexander, 1950; Binger, 1951; Dunbar, 1947; Ferris et al., 1948; Hambling, 1959; Hamilton, 1955; Harris and Forsyth, 1973; Harris et al., 1953; Hinkle and Wolff, 1962; Jenkins, Rosenman, and Friedman, 1968; Kemple, 1945; Matarazzo, 1954; Mills, 1959; Mordkoff and Parsons, 1968; Reiser, Ferris, and Levine, 1937; Rennie, 1939; Rosenman et al., 1968; Saslow et al., 1950; Saul, 1939; Shapiro, 1960; Sokolow et al., 1962; Syme, 1968; Wolf and Wolff, 1946; Wolf et al., 1955; Wolff, 1953). It is this ambivalence in hypertension that forms the nexus of psycho-diagnostic study of the disease: the hostility that is neither expressed nor repressed, and the anxiety that as product of the conflict, becomes a secondary, generalized response (Binger, 1951; Graham, 1972; Hambling, 1959; Saul, 1939; White, 1964).

Descriptions of the hypertensive personality fit fairly well into the specificity-of-attitude formulation (Grace and Graham, 1952); namely, that the individual feels threatened by personal interaction and must be ever watchful and defensive (Graham et al., 1962). It should be pointed out, however, that gastrointestinal ulcers, rheumatoid arthritis, ulcerative colitis, Raynaud's disease, migraine, and vasovagal fainting are

all presumed psychosomatic disorders in which these same personality variables of inhibited hostility and anxiety figure prominently (Alexander, 1950; Graham, 1972). This being so, there does not appear to be a clear-cut specificity-of-attitude that can be correlated with any one particular organic dysfunction.

The apparent trait constellation in hypertension might nevertheless be considered a constellation of chronic emotions (Graham, 1972). This constellation of chronic emotions not only exists in conjuction with hormonal and neurophysiological states that may be pathologically altered, it may also be both stimulus and response to those somatic states (Ausubel, 1966; Tepperman, 1968). In this sense, it is possible that both the behaviors and the physical symptoms found in hypertension are forms of maladaptive compensation (Ausubel, 1966).

Autonomic Response Specificity in Essential Hypertension

Experiments directed to the question of autonomic response specificity (Lacey and Lacey, 1958; Lacey, Bateman, and VanLehn, 1953) have demonstrated that pressor hyperreactivity is a characteristically dominant response in essential hypertension (Engel and Bickford, 1961; Moos and Engel, 1962). This evidence and observations of skeletal muscle behavior in hypertensive humans suggest that it may be the patterning of autonomic and motor responses that differentiates essential hypertension from other psychosomatic disorders (Buss, 1966; Brod, 1962; Wolf et al., 1955). The concept of patterning has been strongly supported by the comparative study of essential hypertension and rheumatoid arthritis (Moos and Engel, 1962), for even though relaxation procedures have shown

that tautness of the skeletal musculature contributes to chronically elevated blood pressure (Datey et al., 1969; Jacobson, 1939; Jacobson, 1940; Wallace, 1970), muscle behavior is clearly not the principal determinant of autonomic response specificity in essential hypertension. Muscle action potential (MAP) recordings of the electromyogram (EMG) and blood pressure readings were taken of individuals with rheumatoid arthritis and of another group of individuals with hypertension during conditioning to meaningful verbal stimuli and during semantic generalization (Moos and Engel, 1962). In the arthritic group, higher EMG activity in symptomatic muscles and less adaptation in these muscles were matched in the hypertensive group by higher and more sustained systolic and diastolic blood pressure, and relative lack of adaptation in blood pressure.

This kind of between-subject variance has also been observed in healthy, adult human subjects monitored for multiple peripheral responses while responding to the same stressful environmental stimuli (Ax, 1953). It has also been observed that normal conscious cats show individual differences in predominance of a particular physiological variable within the context of generalized sympathetic arousal during stimulation by chronically implanted electrodes in the hypothalamic area for the defense reaction (Hilton, 1965).

It is probable that idiosyncratic psychophysiological response patterns in all organisms are innately elicited by emotionally provocative stimuli, and are either altered or maintained over time by varieties of reinforcement according to the principles of instrumental learning (Benson et al., 1969; Benson et al., 1971; Blanchard and Young, 1973; Brener and Kleinman, 1970; DiCara and Miller, 1968a; DiCara and Miller,

1968b; Dicara and Weiss, 1969; Herd et al., 1969; Katcher et al., 1969; Miller and Banuazzi, 1968). It must be said, however, that although organisms evidently have an inherent capacity to be continuously modified and developed in all their life systems by learning (Lang, Rice, and Sternbach, 1972), base levels of individual response, in contrast to magnitude of change in response, tend to be consistent over time except as chronic pathology changes the innate state (Johnson, Hord, and Lubin, 1963; Oken et al., 1962; Wenger et al., 1960).

Correlation Between Specificity-of-Attitude and Autonomic Response Specificity

Investigators have sought to establish a link between specificity-of-attitude and autonomic response specificity in several different ways. The steps in this process will be described in what would seem to be a logical, if not necessarily chronological, order.

First, there have been attempts to clearly distinguish between the states of anger and depression. Studies of frustration in normal adults (Funkenstein, King, and Drolette, 1954) have defined anger as "anger-out", meaning inhibited, but nonetheless outward-directed anger, and depression as "anger-in", or anger that is both inhibited and directed towards the self.

Secondly, experiments have been designed to differentiate different emotions physiologically. Ax (1953) demonstrated that the emotions of anger and fear produce different physiological patterns of response in normal human subjects exposed to anger-provoking and fear-provoking situational stress. In fear, subjects showed greater increments in levels of skin conductance, in number of muscle tension peaks (frontalis

muscle), and in respiration rate. There were greater increases in heart rate and systolic blood pressure in fear than in anger, but these differences did not reach significance. In anger, in contrast to fear, subjects showed elevated diastolic blood pressure, decreased heart rate, increase in muscle potentials, and increase in number of galvanic skin responses (GSR).

J. Schachter (1957) published a study undertaken partly in collaboration with Ax (1953), in which he tested the blood pressure response in hypertensive, and potentially hypertensive, persons in the experimental situation of the Ax study, with the data from the subjects of that study serving as the control, and with the added variable of the cold-pressor test as a pain stimulus. Blood pressure response in fear, anger, and pain proved to be relatively greater in the hypertensive subjects, as did the intensity of their emotional reactions, expressed either verbally or in motor behavior.

The hypothesis that elevation in blood pressure and "generalized physiological over-response" (Oken et al., 1962) result from inhibited anger has been tested. Blood pressure, heart rate, and verbally expressed or behaviorally displayed anger were recorded in a normotensive, mixed group of psychiatric patients during stressful interviews over a 4 day period. Increase in cardiac output occurred most characteristically, but those subjects who tended to inhibit their anger had higher diastolic and lower systolic blood pressure than those who gave free expression to their emotions (Oken, 1960; Oken et al., 1962).

Third, research on the catecholamines growing out of investigations of autonomic balance (adrenergic/cholinergic) (Eppinger and Hess, 1910; Wenger, 1941) uncovered individual differences in internal secretion of

norepinephrine and epinephrine within mixed psychiatric patient groups (Funkenstein, Greenblatt, and Solomon, 1952). These differences were detected by the use of intramuscular injection of the parasympathetic stimulant, mecholyl (acetyl betamethyl choline), and intravenous injection of epinephrine, alone and in combination with mecholyl. This technique, developed by Wenger (1941), proved useful in determining favorable prognosis for electroconvulsive shock therapy (Funkenstein, Greenblatt, and Solomon, 1948; Funkenstein, Greenblatt, and Solomon, 1950; Funkenstein, Greenblatt, and Solomon, 1951).

Continued, psychologically oriented research on the catecholamines established that high urinary excretion levels of norepinephrine and its metabolites generally correlated well with either active, aggressive, or agonistic behavior, and that epinephrine and its metabolite, metanephrine, seemed most typically to be excreted in states of fear, depression, and anxiety (Elmadjian, Hope, and Lamson, 1958; von Euler and Lundberg, 1954; Hoagland, 1961). Silverman and Cohen (1960) found positive correlation between emotional state, blood pressure response, g-tolerance and urinary excretion levels of catecholamines in human subjects undergoing projective testing [focused thematic test (FTT)] and centrifuge stress. Significant correlations were found between anxiety, systolic hypotension, low g-tolerance, and high excretion levels of epinephrine on the one hand, and impulsiveness, aggressiveness, relatively high systolic blood pressure, high g-tolerance, and high excretion levels of norepinephrine on the other.

Injection and infusion studies of the catecholamines in human subjects have provided further evidence of the autonomic stereotype of epinephrine and norepinephrine, the general patterns of emotional and

physiological response remaining true. Ax (1960) essentially replicated the physiological response patterns of fear and anger (Ax, 1953) with injections of norepinephrine bitartrate and epinephrine in 5 of the subjects of the original study. There were anomalies in the results (e.g. a sharp rise in diastolic blood pressure following injection of epinephrine) that were considered to be reactions to the injection procedure itself.

The cardiovascular effects of norepinephrine and epinephrine infusion were observed in patients with essential hypertension and in a normotensive group (Goldenberg et al., 1948), showing that hypertensive persons were more responsive to norepinephrine. In normal subjects, Ax et al. (1969) found that cardiac output showed greater increase in response to epinephrine infusion and greater decrease in response to norepinephrine, and that greater skin vasoconstriction (inferred from finger pulse pressure) resulted from norepinephrine infusion. The findings on cardiac output and skin blood flow in this study generally substantiated the results of a report on autonomic response patterns in response to epinephrine and norepinephrine infusion in normal persons by Wenger et al. (1960).

The Significance of Genetics to Behavioral Specificity

Investigation of pepsinogen secretion (Mirsky, 1958) and of pupillary and vascular dilatation (Richmond and Lustman, 1955) in human neonates has given experimental support to the belief that patterns of autonomic response may be inherited (Buss, 1966; Hines and Brown, 1933; Sivertsson, 1970). The belief has been further substantiated by the

discovery of high heritability of hypertension in humans (h^2=0.76 for systolic pressure) in monozygotic twin studies (Hines, McIlhaney, and Gage, 1957; Simon et al., 1968; Vander Molen et al., 1970). The very fact that strains of rats, such as SHR, have been selectively bred to become hypertensive also supports the premise of a strong hereditary component to the disease (Knudsen et al., 1973). It will be remembered that hypertension is believed to be polygenetically determined in both man and SHR (Ch.II, p.21).

At present, speculation on the etiology of essential hypertension is centered on the "trigger mechanism" that leads to its expression. It is conceivable that a genetically determined predisposition to hypertrophy in smooth muscle exists in certain individuals and that this predisposition is the primary cause rather than the consequence of high blood pressure (Folkow et al., 1970a; Folkow et al., 1970b; Sivertsson, 1970). It is likewise conceivable that the inherited trigger mechanism might be an exaggerated pattern of centrally regulated sympathetic discharge that, in the course of time, raises and maintains the pressure load at the medullary regulatory centers and throughout the entire cardiovascular system (Buss, 1966; Hines and Brown, 1933; Folkow and Neil, 1971; Sivertsson, 1970). It has been seen (Ch.II, p.20) that this pattern of central nervous activity is mediated by high concentrations and activity levels of norepinephrine, and that it produces aggressive, hostile behavior in SHR. Extrapolation of these data to human emotional behavior does not seem invalid since hypertension in this animal is deemed such an excellent analogue of human hypertensive disease.

Summary and Conclusions

The personality variables in essential hypertension, although not unique to the disease, do seem to be associated with an autonomic response specificity in which the blood pressure response is predominant and a chronic norepinephrine-like state of arousal exists. There are perhaps chronic attitudes in hypertension as well. Although external circumstance must surely have some part in their formation, there are indications from animal studies that inheritance may play a part in an excitability of temperament that is corticohypothalamic in origin. There is also an hypothesis from observations of both animal and man that increased peripheral resistance may be brought about by an inherited tendency to smooth muscle hypertrophy.

Essentially, then, the hypertensive state describes a closed system that is vulnerable to the dangers of positive feedback. As part of this system, the attitudes and/or emotional behaviors of the hypertensive organism can be thought of as both genesis and product of a complicated pathology.

CHAPTER VI

THE SUMMARY AND CONCLUSIONS

This paper has been a review of some of the published literature on essential hypertension. It has dwelt with what have seemed to be six of the more distinguishing features of the illness. In the process of defining these features, there has been an attempt to show that a psychosomatic disorder can be examined to advantage as an interrelationship between systems. It has in fact become apparent that there is interdependence and some evidence of synergism between the psychological and physiological systems that have been chosen for discussion. Sympathetic (noradrenergic) and renal-adrenocortical function, the baroceptor reflex, smooth muscle activity in all body tissue, skeletal muscle behavior, and prevailing psychological states all seem, in essential hypertension, to reveal degrees of either heightened reactivity, or of pathologic modification of tissue and tissue processes that have developed from overreactivity.

It is presumed that these interrelationships of mind and body interact with the more global influences of genetic predisposition and total life experience. These are influences that incorporate such variables as specific organic susceptibility, perception of self, and the complexities of motivation. It has been suggested, for example, that smooth muscle and centers of the brain that regulate emotionally motivated behavior may both manifest the demonstrable heritability of hypertension. Given

the genetic factor, essential hypertension may be a form of adaptation by the whole person to many different sources of internal and environmental stimulation. The disease may be even more aptly described as a form of maladaptation, for it seems characterized by attitudinal and physiological overcompensation. It will be necessary to define, ever more precisely, how central and peripheral systems interact, and to identify the interplay of genetics and environment in mechanisms that are psychologic, neurologic, metabolic, and hormonal.

Some of the symptoms of essential hypertension are probably the products of conditioning. This way of evaluating certain elements of the disorder not only extends our understanding of them, but also suggests directions for therapy. Techniques continue to be developed whereby both emotional and visceral behaviors may be modified. These therapies hold promise for the individual suffering from perhaps the most bewildering of maladies, one in which the afflicted finds himself both agent and victim of his own pathology.

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