Herbert Weiner

AUTONOMIC PSYCHOPHYSIOLOGY:

PERIPHERAL AUTONOMIC MECHANISMS AND THEIR CENTRAL CONTROL

American Handbook of Psychiatry

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Introduction

Social and psychological stimuli, tasks and constraints and the physiological responses they engender in human and animal subjects, are mediated by hormonal, autonomic, and neuromuscular mechanisms. For this reason, some data and concepts about the organization and function of the autonomic nervous system (ANS) in particular will be presented here in order to add meaning to the psychophysiological relationship which will be outlined in Chapter 23. Little discussion of the control of the neuromuscular system will take place in this Chapter because there is only limited information available about the control of electromyographically recorded activity from muscle. In addition, a full discussion of the neuromuscular transmission would lead the reader too far afield from the main interests of the clinical psychophysiologist.

By definition, the psychophysiologists attempt to record physiological changes after social and psychological stimulation in the intact subject with

an absolute minimum of interferences such as the taking of blood samples and intubating blood vessels. At the same time, it behooves the investigator to make absolutely certain that his measurements, which are indirect, validly reflect changes in the functioning of the system or organ under study. Once having made certain of the change he is measuring, he must ascertain that the change occurred from a steady-state baseline. This steady-state probably reflects the product of a number of different physiological parameters: the intrinsic activity of the organ (the denervated heart beats regularly and slowly); the tonic innervation of the organ through the autonomic nervous system which solely modifies the intrinsic rhythm; the effect of neurotransmitter release into the circulation from autonomic nerve endings and the adrenal medulla; the rate of reuptake and metabolism of the free transmitter; the regulation of neurotransmitter biosynthesis, release, and metabolism by the adrenal gland which is under combined hormonal and neural control; and the nature and state of the receptor mechanism for the neurotransmitter at the end organ.

Once the steady-state is disturbed by environmental and psychological variables, dynamic physiological changes begin to occur. The change in physiological function—for instance, an increase in the heart rate from a steady-state level—may be the combination of a large variety of physiological factors, such as a change in cardiac filling, and phasic adrenergic discharge affecting, for example, the sino-auricular node, and increasing

atrioventricular conduction velocity, etc. This phasic discharge may, in turn, be regulated by complex central-nervous circuits which lie in all parts of the brain, but particularly in the midbrain, hypothalamus, brain stem, and spinal cord.

Among the important *psychological* parameters affecting acute physiological changes are: the novelty of the stimulus; the expectations of the investigator and the subject; anticipation by the subject of the task ahead; individual response tendencies which, in part, are determined by earlier experiences of the subject; the length of time the subject is given before engaging in a specific task; and the nature and duration of the task or stress.

The kinds of physiological responses which prolonged stresses elicit are different, and are mediated by different mechanisms, than those which are elicited by acute psychological stresses.

With the exception of the EEG,[1] evoked and other potentials, and electromyographic responses studied by psychophysiologists, all the physiological functions which psychophysiologists record depend primarily on autonomic regulation and control. For example, changes in pupillary size, salivary flow, heart rate, blood pressure, respiratory rate and volume, blood flow through the skin, sweating, gastric motility and secretion, urinary flow, or uterine contraction are to a large extent under autonomic control, although

the hormonal regulation of a function also plays a role. Uterine contractility, for example, depends on the stage of the menstrual cycle and the amounts of circulating estrogen and progesterone, etc., while the contractile responses of the pregnant uterus to neural stimuli differs from the nonpregnant one.

This Chapter also attempts to review new information about the autonomic nervous system which has changed our concepts about its functioning.

It used to be said that the sympathetic-adrenergic system mainly discharged as a unit, especially in situations in which the organism responded with the emotions of fright or rage. It used to be believed that the parasympathetic-cholinergic nervous system was mainly organized for discrete and localized discharge and not for mass responses; from a teleonomic point of view, it was considered that it subserves conservative and restorative processes.

These generalizations, however, do not hold in the light of new evidence. Discrete sympathetically mediated responses can be elicited by operant conditioning. Therefore, only under some circumstances does mass discharge of the sympathetic nervous system occur.

Secondly, it is now quite clear that the autonomic nervous system is not only “involuntary.” In fact, it can be manipulated by operant techniques which

a subject may learn. Furthermore, some "involuntary" functions (such as the alpha rhythm of the EEG) cannot only be recognized but also controlled by their owner. Subjects can also be "taught" to lower their blood pressure. In other words, voluntary control can be achieved over "involuntary" function.

Another new discovery indicates that, in some instances, the transmitter substance of the postganglionic sympathetic nervous system is not norepinephrine but acetylcholine. Therefore, it cannot be correctly assumed that the sympathetic nervous system is exclusively "adrenergic." For example, vasodilatation in skeletal muscle is, in part, brought about by a sympathetic cholinergic system.

In addition, the effects of the norepinephrine release at postganglionic synapses and of epinephrine are, in part, determined by the nature of the receptor. Norepinephrine and epinephrine can cause either excitation or inhibition of smooth muscle, depending on the site and to some extent on its amount. For example, sympathetic discharge produces contraction of the radial muscle of the iris, constriction of the blood vessels of the skin mucosa and lungs, contraction of pilomotor muscles in the skin and the intestinal sphincters, but it also brings about relaxation of the ciliary muscle of the eye, of the bronchial muscles of the lung, and detrusor muscles of the bladder. Where contraction is produced, physiologists classify the receptor as belonging to the a-type, where relaxation occurs they call it the β-type. Some

catecholamines mainly affect one type of receptor to produce excitation and others to produce inhibition. Thus, norepinephrine is the most powerful, excitatory catecholamine and mainly affects a-receptors, whereas isoproterenol exhibits the opposite effect. Epinephrine has both excitatory and inhibitory properties. The majority of adrenergic blocking agents act selectively on the excitatory or inhibitory effects of the catecholamines, and can thus be classified as *a*-(e.g., phenoxybenzamine) or *β*-(e.g., 3.4-dichloroisoproterenol) blocking agents.

Cardiac nodes and muscles respond to an increase in sympathetic discharge or the catecholamines, by an increase in rate of discharge and contractile vigor respectively, but have the properties (as defined by their responses to pharmacological agents, i.e., isoproterenol) of the *β* -receptors.

The Autonomic Nervous System: Anatomy and Physiology

The more we know about the functioning of the ANS, the better are we able to grasp the meaning of psychophysiological correlations. This leading statement has often been contradicted by psychophysiologists, many of whom tend to be concerned only with demonstrating empirical relationships, or to use psychophysiological techniques to study “covert” behaviors. They argue, with some conviction, that it is not absolutely necessary to understand mechanisms, if it can be demonstrated that training techniques affect

physiological function which has been disturbed in disease states, e.g., to lower blood pressure in a patient with essential hypertension by operant techniques.

It is our conviction that such a pragmatic approach evades the basic question of why the blood pressure became elevated in essential hypertension. Although we cannot give an answer to this question, it is fairly widely accepted that an elevated diastolic pressure is but a symptom of essential hypertension, not the disease itself, and represents the end product and an adjustment to altered functions in several different systems—e.g., the brain, adrenal gland, kidney, arteriolar tree, etc.

Therefore, it would seem to be an omission not to be aware of the role of the ANS in a wide variety of bodily functions, including important metabolic and behavioral ones.

Anatomy of the Autonomic Nervous System

All structures within and on the surface of the body are innervated by the autonomic nervous system. Obviously, the main motor nerves to skeletal muscle belong to the "voluntary" nervous system, but blood flow within such muscle is autonomically regulated.

One major difference between the motor nerves of the autonomic and

the neuromuscular systems is that synaptic connections between the preganglionic and postganglionic fibers of the autonomic system are made outside the neuraxis in a system of ganglia. Emerging from these ganglia, the postganglionic "motor" nerves are further organized into a system of peripheral plexuses, the constitutent fibers of which are largely unmyelinated and, therefore, have much slower conduction velocities. They reveal other characteristics than the motor neurons of the neuromuscular system. Denervation of autonomically innervated structures does not preclude their function in the same manner that the function of striated (noncardiac) muscle does.

The two divisions of autonomic efferent fibers—the sympathetic and parasympathetic —innervate the heart, and the same glandular and other structures which are composed of smooth muscle. Traditionally, this arrangement has led to the concept, very popular in psychophysiology, that their functions are antagonistic. Actually, the level of activity in an effector organ at any one moment is the algebraic sum of many influences, i.e., a decrease in adrenergic excitation, while keeping cholinergic excitation steady, may appear as if cholinergic excitation had increased. In fact, recent advances have forced a modification of the old view. For instance, vasodilatation in muscle is mediated by a *sympathetic,* postganglionic cholinergic mechanism. The algebraic sum is also influenced by circulating neurohumors.

The efferent cells of preganglionic sympathetic fibers lie in the intermediolateral columns of the spinal cord from the level of the eight cervical to the second or third lumbar vertebra. Their axons pass with the anterior nerve roots to a series of twenty-two interconnected, paravertebral ganglia where they form synaptic connections with postganglionic sympathetic fibers. Among the most important of these fibers are the ones passing from the superior cervical ganglion to the eye, the lacrimal, submaxillary, and parotid glands, and the heart. The heart also receives postganglionic sympathetic innervation from the middle and inferior cervical ganglia. The superior cervical ganglion also sends postganglionic fibers up the carotid canal to innervate the pineal gland. The biosynthesis of melatonin in that gland is regulated by the light-stimulated release of norepinephrine from the terminals of these sympathetic fibers.

The receptors of the radial muscle of the iris are of the a-type; an increase in sympathetic activity produces contraction, /8-receptors obtain in the ciliary muscle of the eye, sinoatrial and atrioventricular nodes, cardiac atria, ventricles, and conduction system of the heart. Excitation therefore produces relaxation of the ciliary muscle, an increase in heart rate and conduction velocity, in the force of contraction of the heart and in the rate of its intrinsic pacemaker.

The stellate ganglion receives its input mainly from T_1 (first thoracic

vertebral level) and sends postganglionic fibers to the heart, lungs, and bronchi whose muscles contain mainly β -receptors which are relaxed by an increase in sympathetic activity. However, the musculature of the lungs also contains α-receptors and is, therefore, subject to constriction by sympathetic excitation.

The celiac ganglion receives sympathetic input from $T_{5\text{-}9}$ through the greater splanchnic nerve which also directly innervates the adrenal medulla. Other ganglionic input comes from the lesser splanchnic ($T_{10\text{-}11}$) and the least splanchnic nerves ($T_{11\text{-}12}$). Postganglionic fibers from the celiac ganglion innervate the liver, bile ducts, gall bladder, splenic capsule, stomach, small bowel, proximal colon, kidney, and ureter. Sympathetic excitation is mediated by /8-receptors in the stomach and intestine to decrease motility and tone, and by α-receptors to contract its sphincters. The capsule of the spleen is contracted by the mediation of a-receptors. Sympathetic discharge induces the biosynthetic enzymes of norepinephrine and epinephrine, so that adrenal-gland levels of these enzymes are raised. On the other hand, dopamine blood levels are raised by an increase in biosynthesis in sympathetic fibers, and not by its liberation from the adrenal medulla.

From the levels of $T_{12\text{-}13}$ preganglionic fibers pass to the superior and inferior mesenteric ganglia. The former innervate the distal colon and rectum to decrease motility and increase the contraction of the anal sphincters; the

latter supplies the urinary bladder whose β -receptors relax the detrusor muscle while a-receptors of the trigone and sphincter are made to contract. Ejaculation of semen is produced by sympathetic activity. The type of receptor in the appropriate muscle is not known.

Fibers from the lower thoracic and the first three lumbar segments also supply the sacral ganglia which send postganglionic fibers to blood vessels, hair follicles, and sweat glands of the legs.

Their postganglionic fibers ("gray rami") are carried in spinal nerves for distribution to blood vessels of the skin, sweat glands, hair follicles and the vessels in skeletal muscle. Except for a double system of receptors in the skeletal muscles of the legs, all of these structures contain a-receptors. Thus, constriction of blood vessels and slight local secretion of sweat glands are produced when these receptors are stimulated.

Anatomy of the Parasympathetic Nervous System

The cells of origin of the parasympathetic nervous system reside in nuclei of the third, seventh, ninth, and tenth cranial nerves, and in the gray matter of the second, third, and fourth segments of the sacral spinal cord. The axons of these cells pass to ganglia which lie close to the organs which they innervate. From the E dinger-Westphal nucleus of the oculomotor nerve, cells pass to the ciliary ganglion whose postganglionic fibers innervate the

sphincter muscle of the iris and ciliary muscle, both of which contract on nerve or ganglionic stimulation.

Excitation of fibers from the nucleus of the facial nerve pass to the sphenopalatine ganglion and thence to the lacrimal gland to cause tears to flow. Parasympathetic excitation produces salivation and vasodilation in the nasal and oral cavity by virtue of outflow from the same nerve via the chorda tympani and ganglia which innervate the sublingual and sub-maxillary gland. The glossopharyngeal nerve sends preganglionic fibers to the otic ganglion from which postganglionic fibers pass to the parotid gland. The motor nucleus of the vagus nerve sends very long preganglionic fibers to all the viscera except the distal colon, bladder, ureter, and genitalia which receive innervation from cell bodies in $S_{2\text{-}4}$, spinal cord segments via the pelvic nerves. The parasympathetic ganglia lie on or in the organs they innervate. Short postganglionic fibers pass to the receptor sites in them. In the wall of the gastrointestinal tract, vagal preganglionic fibers synapse around the ganglion cells of the plexuses of Auerbach and Meissner. Parasympathetic excitation produces dilatation of blood vessels in most organs; other muscles such as those in the bronchial tree, stomach, intestine, gall bladder, and the detrusor muscle of the bladder are made to contract, or their tone and motility is increased by parasympathetic discharge. A decrease in heart rate to the point of atrioventricular (AV) block is produced by vagal discharge which also reduces conduction velocity in, and the contractile force of the

heart. Secretion of all exocrine glands is increased by parasympathetic discharge. Penile erection is produced by it.

In other words, most organs are doubly innervated, except for the adrenal medulla, pilomotor muscles, many vascular beds in skin, and muscle and the sweat glands of the skin.

Neurotransmission in the Autonomic Nervous System

Central to our understanding of the function of the autonomic nervous system is the concept of neurotransmission. Autonomic nerve impulses elicit responses in smooth and cardiac muscle, exocrine and some endocrine glands, and postsynaptic neurons by the liberation of specific, identified chemical substances. Great strides have been made in our understanding of the storage, release, biosynthesis, and removal of these substances. But our understanding of the receptor mechanisms by which these substances exert their effect postsynaptically is just barely beginning.

Acetylcholine is the neurotransmitter of all *postganglionic parasympathetic fibers* and a few *postganglionic sympathetic fibers,* such as those leading to the sweat glands and the sympathetic vasodilator fibers. *Preganglionic sympathetic* and *parasympathetic fibers* release acetylcholine. A branch of the greater splanchnic nerve which innervates the adrenal medulla also releases acetylcholine, and may influence the biosynthesis of

norepinephrine and epinephrine in this gland by the induction of the enzyme, tyrosine hydroxylase (TH).[2]

Norepinephrine is the principal sympathomimetic substance in *postganglionic sympathetic nerves* (It may also play a role as an inhibitory neurotransmitter in clearly defined tracts in the brain such as the median forebrain bundle and a tract from the locus coeruleus to Purkinje cells in the cerebellum. Other amines such as histamine, serotonin, and certain amino acids, y-aminobutryic acid and glycine—may also play unidentified roles in central neurotransmission.)

The effect of the neurotransmitter substances on end organs and postsynaptic fibers is in part a function of whether they produce excitation or inhibition; the intrinsic activity of the innervated structure; the state of the receptor of that structure; and the rates of synthesis, release, reuptake and enzymatic destruction or diffusion of the neurotransmitter. All these factors determine the ultimate response of the end organ whose activity the psychophysiologist wishes to measure.

There are, of course, fundamental differences between the responses of autonomically innervated structures and those innervated by striated muscle. Seeing that psychophysiologists are interested in responses from both types of structures, these differences might be worth dwelling upon. Preganglionic

autonomic fibers are typically myelinated and have the properties of B-fibers, whereas motoneurons (A-fibers) have a larger diameter and thus a much greater conduction rate and shorter spike duration and absolute refractory period. Postganglionic sympathetic axons are unmyelinated (sC-fibers), have smaller fiber diameters, the slowest conduction velocity (in comparison to A and B fibers) and a relatively long spike-potential and absolute refractory period.

The responses of the effector organ is, in part, also the product of relatively slower destruction and thus more prolonged action of the transmitter.

Skeletal muscle responds to a single stimulus to its motor nerve by a brief solitary event—the action potential of the muscle, measured by EMG (electromyogram), followed by the muscle twitch which can be recorded as a smooth increase and then decrease in muscle tension. When a sympathetic axon is stimulated, a muscle action potential shows an initial deflection followed by a series of asynchronous deflections which continue for several seconds after repolarization of the nerve fiber has occurred. The tension record of the smooth muscle shows a gradual and prolonged buildup associated with each muscle action potential change. The transmitter agent remains and continues active long after nerve action has ceased.

Synaptic Transmission

The same mechanism of axonal transmission applies in postganglionic adrenergic and cholinergic fibers. The nerve-action potential consists of a self-propagated reversal of negativity of the axonal membrane (seen from the point of view of the internal potential of the axon) as a result of the admission of sodium and egress of potassium ions. When the action potential arrives at the presynaptic terminal either excitatory or inhibitory transmitter is released by a mechanism that is not wholly understood.

In all probability, and based on the model of neuromuscular transmission, there is a continuous quantal release of transmitter during the resting state which does not, however, produce enough depolarization of the post-synaptic membrane to reach the "firing level." When the "firing level" is reached, a postsynaptic action potential is generated.

When the excitatory transmitter combines with postsynaptic receptors, a localized depolarization occurs which can be recorded by means of an intracellular electrode, as an excitatory postsynaptic potential (EPSP)—that is, a decrease in negativity of the direct current (DC) potential by virtue of an increase in permeability of all ions, particularly those of sodium and potassium. Inhibitory transmitters produce the opposite effect—that is, hyperpolarization with an increase in negativity of the DC (the inhibitory postsynaptic or IPS) potential due to an increase in permeability to potassium

and chloride ions.

When the “firing level” has been reached, a propagated action potential is produced in the nerve, and a muscle action potential in most skeletal and cardiac muscle. In certain types of tonic skeletal muscle and in smooth muscle in which propagated impulses do not occur, an EPSP initiates a local contraction, while in gland cells it initiates secretion, probably by means of the induction of enzymes.

Acetylcholine

The excitatory transmitter in autonomic ganglia is acetylcholine. It is probably synthesized by choline acetylase in the region of axon terminals and stored in highly concentrated, ionic form in synaptic vesicles. Acetylcholine is rapidly removed presumably by a specific and specialized enzyme, acetylcholinesterase, which splits the molecule into choline and acetic acid, once acetylcholine is liberated into the synaptic cleft. Acetylcholinesterase, on the other hand, is located at the surface in the infoldings of the postjunctional membrane, and in the subneural apparatus of the motor end plate of most skeletal muscle. In the superior cervical ganglion of the cat, the enzyme is located external to the presynaptic membrane.

Modification of synaptic transmission at ganglia is produced by epinephrine and norepinephrine. They can depress transmission in low

doses, and in even lower concentrations enhance it. Thus, it has been proposed that the regulation of transmission may occur by an interaction of acetylcholine and these two catecholamines.

In sympathetic postganglionic fibers, Burn has suggested that acetylcholine is released on stimulation which, in turn, causes the release of norepinephrine to act on effector organs. However, this hypothesis which would explain many diverse observations is not generally accepted. If confirmed, it would give acetylcholine a role additional to that of a neurotransmitter.

In fact, such a role is suggested by the fact that acetylcholine, choline acetylase and acetylcholinesterase are present at a variety of nonsynaptic sites. It has also been suggested that it plays a role in axonal conduction, in the regulation of membrane transport and permeability, and as a local hormone.

Physiological Effects of Acetylcholine

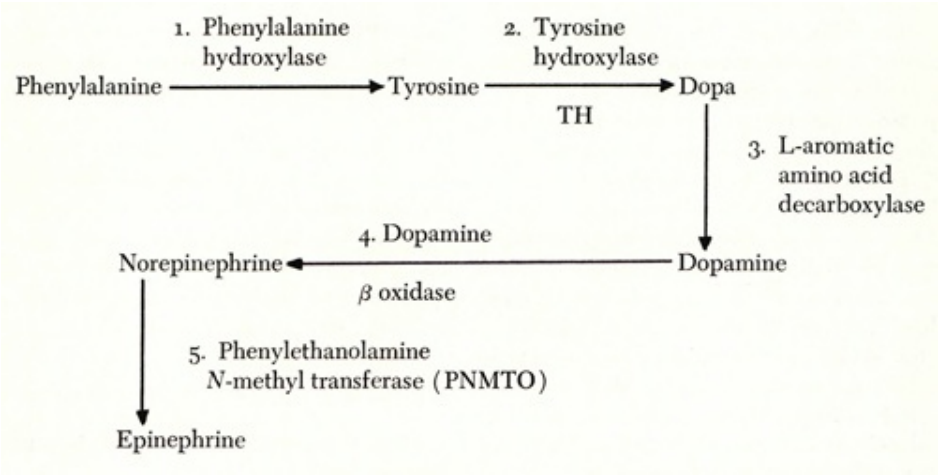
All of the physiological effects of acetylcholine are very brief because of the speed with which it is hydrolysed by acetylcholinesterase. The effects noted are mainly those that might be expected after stimulation of postganglionic parasympathetic nerve fibers.

In the cardiovascular system, it may produce vasodilatation, a decrease in blood pressure, bradycardia, arrhythmias, including partial or complete atrioventricular block, and ventricular standstill, etc. But most of these effects are counteracted because of the simultaneous release of catecholamines by the adrenal medulla. In fact, in man, the drug has to be given in large doses and rapidly, to produce these and other effects such as lacrimation, salivation, sweating, cough, and vomiting which are due to increase in tone, amplitude, and peristaltic activity of the stomach.

Catecholamines and Adrenergic Transmission

We owe to Elliot the concept of adrenergic transmission, to von Euler the identification of norepinephrine as the adrenergic transmitter, and to Axelrod the explanation of the metabolic disposition and some of the steps in the biosynthesis of norepinephrine and epinephrine. From the point of view of integrative behavioral biology and psychophysiology in particular, recent advances in understanding the role of the catecholamines in the brain and periphery have wide-ranging significance.

Epinephrine is synthesized in five steps from the amino acid phenylalanine:



The enzymes involved in this biosynthetic pathway are not specific and it may be that other biosynthetic steps to epinephrine are possible. Furthermore, the enzyme L-aromatic amino acid decarboxylase also participates in the synthesis of important biogenic amines such as histamine, tyramine and serotonin.

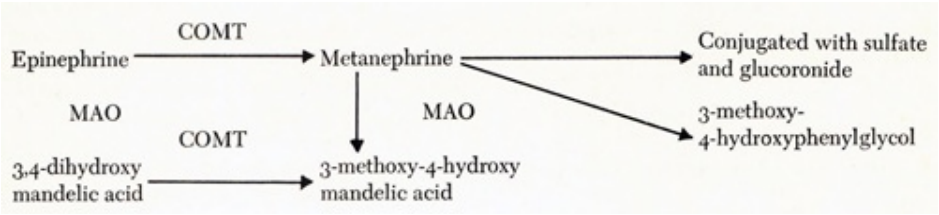
Also of interest is that epinephrine, the end product of biosynthesis, inhibits tyrosine hydroxylase (TH) while TH is induced trans-synaptically and by cortisol. In the same manner PNMT is induced, while dopamine is liberated into the blood stream by adrenergic nerve endings.

Once synthesis has occurred norepinephrine is stored in the terminals of postganglionic sympathetic fibers and brain, while epinephrine is thought largely to be localized in chromaffin cells, particularly of the adrenal medulla.

Both are stored as catecholamine-adenosine triphosphonucleotide salts in storage granules. During their synthesis, the biosynthetic step from dopa to dopamine takes place in the cytoplasm of nerve terminals. Dopamine enters the granules of postganglionic nerves and the adrenal medulla, and is then converted into norepinephrine. In the adrenal medulla, norepinephrine leaves the granules, is converted to epinephrine in the cytoplasm and reenters another set of granules where it is stored. After nerve stimulation and when norepinephrine appears in the blood stream, about half is taken up again and stored intracellularly in neurons, and the other half is rapidly degraded by two enzymes, monoamine oxidase (MAO) and cate-cholamine-O-methyl transferase (COMT), to produce 3,4-dihydroxymandelic acid (by MAO), 3-methoxy-4-hydroxymandelic acid (by COMT), and normetanephrine (by COMT). Normetanephrine is further degraded into 3-methoxy-4-hydroxyphenylglycol by MAO, and conjugated with sulfate or glucoronide.

The mechanism of release of norepinephrine by the nerve action potential is as yet unknown (see above). In the adrenal medulla, preganglionic fibers release acetylcholine which may combine with receptor sites at the surface of the chromaffin cells, following which calcium ions may enter these cells to mobilize stored catecholamines.

The fate of released epinephrine is similar to that of norepinephrine according to the following scheme:



Physiological Effects of Adrenergic Transmitter Substances

Catecholamines can produce powerful excitation and inhibition of smooth muscle, depending on which muscle it acts and in which dosage. As mentioned in the introduction, norepinephrine's action is chiefly excitatory and isoproterenol's chiefly inhibitory; epinephrine has equivalent excitatory and inhibitory effects. In the CNS norepinephrine is postulated to be an inhibitory transmitter.

Physiological Effects of Epinephrine

Epinephrine and norepinephrine have different effects on heart rate, epinephrine being more likely to increase it. Both increase the reflex vagal tone through stimulation of mechanoreceptors in the carotid sinus and aortic arch; but the vagal afferent activity after epinephrine is less than after norepinephrine. Furthermore, epinephrine has a more potent effect in stimulating the β-receptors of the heart to keep the blood pressure comparatively low. Epinephrine also reduces peripheral resistance when compared to norepinephrine. The net effect is that norepinephrine tends to

increase heart rate less, but to increase diastolic and systolic blood pressure and peripheral resistance more. In fact, the main effect of epinephrine is to raise the systolic blood pressure, the mean pulmonary-artery pressure, stroke volume, cardiac output, and coronary blood flow. It is well known that it may cause cardiac arrythmias (especially premature ventricular contractions). Muscle blood flow is greatly increased to the detriment of the blood flow in the skin which is much reduced. Splanchnic blood flow (especially hepatic flow) is increased by it, as are oxygen consumption, blood sugar, lactic acid levels, free fatty acids, plasma cholesterol, phospholipids, and some lipoproteins.

The chief effect of epinephrine is to constrict arterioles, thereby raising the blood pressure. But the action of epinephrine on other smooth muscle depends on the type of epinephrine receptor involved. Bronchial smooth muscle is dilated by it and gastrointestinal muscle relaxed or inhibited. On the other hand, the splenic capsule is contracted by epinephrine, partly accounting for the increase in circulating red blood cells following stress, or hemorrhage.

The behavioral effects of epinephrine injected into human subjects are headache, apprehension, restlessness, and tremor. Such effects are, however, not always produced in all subjects. Much depends on the prevailing mood of the subject, the circumstances under which the drug is given, and what kinds

of previous experiences are aroused in the subject.

Physiological Action of Norepinephrine

In contrast to epinephrine, norepinephrine acts mainly on α-receptors except for its action on the β-receptors of the heart. It has much fewer metabolic effects than epinephrine, although in some cells it stimulates the induction of adenylcyclase and thus cyclic AMP in the same manner as epinephrine does. Hyperglycemia is produced by norepinephrine. As mentioned earlier, its cardiac effects are mainly to increase diastolic blood pressure, although systolic blood pressure is also increased; cardiac output remains unchanged or is decreased. Blood flow is reduced through the brain, kidney, liver, and skeletal muscle by virtue of its vasoconstrictor action, while coronary blood flow is increased. Bradycardia is produced reflexly, by norepinephrine; it may cause cardiac arrhythmias.

Integrative Autonomic Mechanisms

Afferent Fibers of the Autonomic Nervous System

A very rich system of visceral afferent fibers, about which still relatively little is known, passes from most organs by means of nonmyelinated fibers into the nervous system via the pelvic, splanchnic, vagus, and other nerves. Visceral afferent fibers make up a major proportion of the total fiber content

of these nerves. About one-half of the splanchnic nerve and even more of the vagus are afferent. Other autonomic afferent fibers from skin structures and blood vessels in striated muscle run centripetally in somatic nerves. The cell bodies of most visceral afferent fibers are located in the dorsal root ganglia of spinal nerves, and in the equivalent sensory ganglia of cranial nerves, e.g., the nodose ganglion of the vagus and the petrosal ganglion of the ninth nerve. Visceral afferent impulses then pass into the dorsal horns of the spinal cord and make synaptic connections with cells in the intermediolateral columns of the spinal cord and in respective cranial nerve nuclei. These cells give rise to afferent fibers which pass to the autonomic ganglia outside the spinal cord.

Autonomic afferent fibers mediate visceral sensation (including pain originating in organs, and are, in part, responsible for "referred" pain). They regulate visceral and hormonal interrelationships and a number of very important respiratory, visceromotor, vasomotor, bladder, and cardiac reflexes. The mechanoreceptors of the carotid sinus and aorta, and the chemoreceptors of the carotid and aortic bodies play a crucial role in the regulation of respiration, heart rate, and blood pressure. These receptors are also involved in the regulation of aldosterone production. Stimulation of the mechanoreceptors at the junction of the thyroid and carotid arteries in the dog inhibits aldosterone[3] production, while a fall in blood pressure increases the output of this steroid. Cutting the thyrocarotid branch of the vagus nerve or occluding the inferior vena cava also increases the production of

aldosterone. In addition, an increase in carotid sinus activity reflexly reduces adrenal catecholamines and antidiuretic hormone output.

The principal arterial baroreceptors are in the aortic arch and carotid sinus. Sudden increases in pressure at the carotid sinus produce a marked increase in frequency of discharge in baroreceptor afferent units, which adapt slowly during continued elevation of pressure. When the pressure is pulsatile rather than constant, the firing rate is greater and in concert with the ascending limb of the pressure change. Afferent activity in the mesenteric nerves may also be increased by perfusion of the duodenum with various food stuffs.

Pulmonary artery baroreceptors are active at normal pulmonary artery pressures and seem to respond mainly to the rate of pressure change with each pulse. Pressure receptors within the atrium and ventricle of the heart also produce two types of afferent neuronal activity. A burst of activity occurs with each atrial contraction and is proportional to its amplitude. Another burst of activity occurs at the time of ventricular systole; in other words, these neuronal units fire proportional to the amount of filling of the pulmonary and systemic venous system. Ventricular receptors provide inputs proportional to changes in systolic ventricular tension.

The arterial chemoreceptors adapt slowly and are mainly influenced by

variations in arterial pO_2, pCO_2, and pH. In the steady-state, there is a continuous discharge which is markedly enhanced by changes in the partial pressure of oxygen in arterial blood, an increase in arterial CO_2 tension, or a fall in blood pressure.

The largest group of vagal afferents comes from the lungs. Stretching of lung inflation receptors in bronchioles and bronchi increases the firing rate of these afferent units; some adapt rapidly, others slowly. Those receptors which are slowly adapting are probably involved in cardiovascular reflexes.

Sensory inputs which travel in somatic, not sympathetic afferent nerves, arise from muscle, the skin of the face, and from viscera and are involved in reflex cardiovascular adjustments which occur with exercise, with facial stimulation, or stimulation of the vibrissae in mammals, during the diving reflex, or visceral irritation and inflammation. Other sources of input, probably mediated by autonomic afferents, arise from the gut, kidney, and bladder.

From the viscera, sympathetic afferents travel either by an extra spinal pathway by way of the sympathetic chain which finally enters the spinal cord, or by way of the ipsilateral spinal fasciculus gracilis, or by a bilateral pathway in the anterolateral region of the white matter of the cord. Some of the pathways of splanchnic origin reach the cerebral cortex via the thalamus,

others pass to the posterior hypothalamus.

In other words, a wide variety of physiological stimuli may influence afferent activity in autonomic nerves, and therefore act as input to the CNS. This input, in turn, interacts with ongoing central activity, so that regulation of a wide variety of peripheral physiological processes occurs. Probably the regulation of blood pressure is the best understood process. A review of the integration and regulation of blood pressure by the nervous system allows one to conclude that only some afferent impulses from mechanoreceptors and chemoreceptors in the heart and major blood vessels, and from the peripheral vascular tree, ascend higher in the nervous system than the medulla and pons. Yet, the vasomotor system of the brain stem is also in turn under the control of two major circuits, one of which—the sympathetic vasodilator system—has in all probability important implications for psychophysiology, as the following account will show.

Organization of Autonomic Reflexes

There is some evidence that autonomic reflex activity may be mediated by autonomic ganglia without the participation of the spinal cord. Preganglionic fibers may give off collaterals to ganglia other than the ones they innervate, so that stimulation of the distal part of a preganglionic fiber isolated from the spinal cord may activate ganglia lying proximally. Although

such evoked activity is known as an “axon” reflex, it is not a reflex in the true sense. Axon reflexes play a part in man in the vasodilatation produced in muscle after contraction. Postganglionic “axon” reflexes have also been invoked to explain local sweat responses to electrical stimulation of the skin, but this response may be due to branching postganglionic fibers; branching occurs near the innervated area so that fibers are sent in all directions. To explain the local sweat response one would have to postulate that stimuli pass antidromically up one fiber and orthodromically down another to cause sweating. Other vasomotor responses of the skin are truly reflex. The afferent arc of the reflex may either be sensory or autonomic.

Visceral autonomic afferents may also produce reflex striped muscle contraction. The abdominal muscles contract when the gut or peritoneum are irritated.

Two main kinds of regulatory mechanisms determine activity in preganglionic autonomic neurons which are maintained in a continuous but variable state of neuronal activity. There are segmental sensory and autonomic inputs through dorsal roots, inputs from pontomedullary neurons, and finally from neural circuits which descend from structures which lie rostral to the brain stem.

In animals whose spinal cords have been cut above the thoracic level, a

state of spinal shock is present and all autonomic reflexes are depressed: Blood pressure and peripheral resistance are low, the urinary bladder is paralyzed, there is no regulation of body temperature and no sweating. But after several weeks, blood pressure levels rise; further rises occur when the skin of the body is touched or pinched below the level of transection. After the "spinal shock" passes off, some body-temperature control and sweating is then reestablished. For example, profuse sweating can be provoked by stimulation of the skin of the body. Urination, defecation, and sexual reflexes reappear and can also be stimulated by stroking the appropriate segments of the body. Chronic decerebrate preparations demonstrate many of the characteristics of the spinal animal with regard to autonomic reflexes, except that arterial pressure is well-maintained, and none of the profound blood-pressure changes, which are precipitated by changes in posture and seen in spinal animals, occur.

Decorticate animals do not show any of the changes in autonomic reflexes seen when more extensive amounts of the nervous system are removed. But these animals do respond to pinching of the skin by "sham" rage behavioral responses and a coordinated massive autonomic (sympathetic) discharge.

Spinal reflexes may be monosynaptic or multisynaptic. Their segmental arrangement is as follows:

Head and neck	T_{1-5}
Pupillodilatation	C_8-T_1
Arms	T_{2-9}
Lacrimal gland	T_{1-3} (sympathetic)
Cardiac acceleration	T_{2-6}
Vasomotor responses, sweating:	
Upper trunk	T_{4-9}
Lower trunk	T_9-L_2
Lower extremities	T_{12}-L_2
Abdominal viscera	T_4-L_2
Genitourinary and anorectal (sympathetic) reflexes	L_{1-2}

Central (Supramedullary) Control of Autonomic Functions

We have seen that autonomic reflexes can either be local or spinal. And it is characteristic of the reflexes in spinal man that they are massive and can be set off by trivial cutaneous stimulation or by temperature alterations. Generally speaking, these very marked responses are attenuated by a complex series of neuronal circuits that course throughout the nervous system. As mentioned earlier, amongst the most important regulatory devices are those to be found in the hypothalamus. At least, and in the case of the body-temperature control system, these mechanisms are arranged in such a

reciprocal manner that negative feedback characterizes their interactions. The posterior and lateral nuclei of the hypothalamus are concerned with the regulation of food intake and temperature; their stimulation leads to massive sympathetic discharge including norepinephrine release.

In the hypothalamus, parasympathetic functions are regulated by midline nuclei in the region of the tuber cinereum and nuclei lying closer to the anterior section. Inputs from the limbic system, cortex, thalamus, and striatum probably modulate the activity of these hypothalamic centers. Stimulation of the perifornical hypothalamus can alone elicit complex emotional behaviors in cats as well as marked sympathetically mediated changes in blood pressure and heart rate, and produce piloerection, etc.

Regulation of Blood Pressure

Central (Brain-Stem) Mechanisms

Before going on to speak about the neurogenic control of blood pressure and peripheral resistance, some general remarks seem in order.

Concepts about the neurogenic control of blood pressure are, in part, limited by the fact that so much of our knowledge of cardiovascular regulation, and the control of blood pressure in particular, derives from observations made on excised organs and anesthetized animals while varying

a single input. Only with the development of new recording methods has it been feasible to make observations on intact unanesthetized animals.

These new techniques eliminate various kinds of artifacts caused, for example, by exposing the heart and lungs in acute experiments, and by anesthesia. In addition, behavioral observations can be made in unanesthetized animals while studying cardiovascular function during exercise or while the animal is interacting with its environment, or during brain stimulation, etc.

Chronic brain stimulation may be used to induce elevations of blood pressure while the animal's behavior is observed. Finally, the hope would be to develop in the future, knowledge of the complete neural and neuronal pathways and the activity in them during such manipulations.

The rapid cardiovascular adjustments which precede and accompany exercise demonstrate a case in point. Whereas these adjustments were once considered to be instigated purely by peripheral mechanisms, it is now believed that the onset of vasodilation and increased flow in muscle, heart rate, and output, etc., at the start of exercise, emanate from the nervous system as an autonomic concomitant to the muscular activity which is under volitional control. These cardiovascular changes at the start of exercise can be abolished by lesions in the fields of Forel, and can be replicated by stimulation

in this area.

In other words, there exist integrated patterns of cardiovascular and motor activities, exemplified by the changes with exercise. Furthermore, these cardiovascular adjustments seem quite specific to a given behavioral activity; other adjustments probably occur with other activities.

In this way one might expect that our ignorance about the neuronal activity which must underlie volitional activity, its correlated affect, and circulatory changes would gradually be dispelled. At present, we know little about the pathways which subserve the emotions of anger, fear, resentment, or the adjustments with exercise.

We also know little about how these emotional states influence homeostatic cardiovascular mechanisms. It is not unlikely that they do so by biasing tonic neuronal activity in complex circuits which run between the mechanoreceptors, the medulla, the midbrain, the hypothalamus, and limbic and cerebral cortices. If different cardiovascular adjustments accompany different behavioral activities, then it is likely that central excitatory influences on the brain stem and hence vasoconstrictor outflow may be quite selective. For example, the sympathetic vasodilator discharge pattern emanating from the hypothalamus is characterized by adrenergic discharge to almost the entire vascular bed, with the exception of skeletal muscle. The

same differential effects occur in vasoconstrictor fibers when activated by cortical stimulation.

The foregoing statements must have some validity in the light of Miller's work and from studies on the organismic response known as the "defense" reaction which was first described by Hess. Sympathetic vasodilation in muscle, increased heart rate, vasoconstriction in vascular beds other than muscle, and increased secretion of catecholamines occur during the defense reaction. Analogous vascular changes are found in man during states of fear, and mental arithmetic, and may occur during anticipatory states.

The behavior of cats when the defense reaction is elicited consists of growling, hissing, running, pupillary dilation, and piloerection. The defense reaction occurs not only when the hypothalamus near the entrance of the fornix is stimulated, but also with stimulation of the dorsomedial amygdala and striae terminalis. The axonal connections between these nuclear regions and others are still not certain. That other connections must exist is suggested by the fact that it is known that the cerebral cortex attenuates the violence of the defense reaction.

The defense reaction is mentioned as an example of a selective vasomotor and behavioral response, and because Folkow and Rubinstein have been able to produce sustained hypertension by mild and intermittent,

daily stimulation for several months in the area of the hypothalamus known to elicit the defense reaction.

Different affective states in man can be accompanied by other and different cardiovascular changes. For example, when a man is hostile or resentful the blood vessels of the gastrointestinal mucosa dilate.

Peripheral Resistance by the CNS

Central to current notions about CNS regulation of blood pressure is that vasomotor regulation is brought about through variations in vasoconstrictor tone. Decreased vasoconstrictor discharge leads to vasodilation, increased discharge to constriction.

Afferent impulses pass from the carotid sinus and aortic arch mechanoreceptors responsive to stretch, and from chemoreceptors which are sensitive to increases in arterial $pC0_2$. Stimulation of the mechanoreceptors leads to vasodilation by inhibition of tonic vasoconstrictor outflow, while stimulation of the chemoreceptors causes vasoconstriction. From the carotid mechanoreceptors, afferent impulses pass via the sinus nerve to the medullary vasomotor centers. At high blood pressures neural discharge is sustained, not phasic, and adaptation may occur to such pressures. However, different firing patterns in the sinus nerve occur and depend on fiber size, because the sinus nerve contains fibers of varying diameters. In view of the

fact that cutting the sinus nerve increases blood pressure, tonic discharge from the mechanoreceptors must also be present.

Afferent impulses also arise from the atrial walls of the heart and ventricles, and from the walls of the great veins. Sensory, especially pain receptors, influence vasomotor tone, possibly via the agency of the medullary center. In addition to input to the vasomotor center from mechano- and chemoreceptors, etc., input may travel in sympathetic afferent fibers to enter the cord.

We owe to Ranson and Alexander most of our knowledge about the vasomotor center. The pressor area lies in the lateral reticular formation of the rostral two-thirds of the medulla, while the depressor center lies medially in the reticular formation and more caudally in the medulla. Tonic inhibition of spinal cardiovascular mechanisms largely emanates from the depressor zone. The neurons of both of these medullary areas are continually active. Tonic excitatory influences from the pressor area impinge on the same spinal neurons. But the synaptic events at spinal vasomotor neurons and the patterns of interactions of the two descending influences on them largely remain unknown. The intensity of the discharge in preganglionic vasoconstrictor neurons must be the resultant of the two descending tonic influences. The frequency of tonic discharge in the thoracic sympathetic outflow is relatively low, and discharge occurs in rhythmic bursts, in concert

with the pulse beat and respiration. Thus, the afferent discharge is probably driven by input to the medullary center from mechanoreceptors in the great vessels and its branches.

The fall in arterial pressure on activation of mechanoreceptors is probably largely accomplished by peripheral vasodilation in muscle, the splanchnic bed, and the skin through inhibition of vasoconstrictor tone.

The mechanisms subserving vasomotor tone have been reviewed above because of the role that mechanoreceptor activity has played in the hypotheses about the maintenance of elevated blood pressure.

Acute and chronic elevations in arterial pressure result from denervation of the sino-aortic region. But, in animals, at least, the resulting hypertension is labile and accompanied by tachycardia. The elevated blood pressure could be lowered in dogs by exercise and hypotensive drugs with considerably more ease than essential hypertension can be in man.

The effects of denervating mechanoreceptors, though instructive in their own right, do not necessarily prove or disprove their role in naturally occurring essential hypertension. There is considerable evidence to suggest that the carotid sinus reflex remains active and functioning in essential hypertension but that the mechanoreceptors adapt to high levels of blood pressure and, therefore, no longer act maximally to reduce pressure levels.

This adaptation occurs in dogs within one to two days after a renal artery is clamped, and is characterized by an increase both in threshold and the range of response of the mechanoreceptors. Recordings from the sinus nerve show a decrease in discharge frequency with changes in pressure in these hypertensive animals. It is not as yet clear what the nature of this adaptation to higher blood pressure is. It is likely to be due to the direct effect of a high systemic pressure rather than to a chemical substance. Such an adaptation to an elevated mean blood pressure would act to sustain it; the decrease in afferent discharge would lead to decreased inhibition of vasomotor tone and therefore further vasoconstriction. These data have led to therapeutic measures designed to counteract the adaptation of the mechanoreceptors. Electrical stimulation of the sinus nerve lowers blood pressure in hypertensive patients.

Stretching of the mechanoreceptors has effects on the CNS in addition to lowering the blood pressure. Bonvallet et al. have distended the carotid sinus while maintaining blood pressure at a constant level, to produce cortical synchronization. They believe that an increase in afferent activity occluded the tonic, corticopetal, desynchronizing influences of the midbrain reticular activating formation. Therefore, one might postulate that if mechanoreceptor adaptation occurs in hypertension, there would be a tendency in the opposite direction, i.e., for cortical desynchronization and behavioral arousal.

An elevated blood pressure may affect the CNS directly and in addition to the effects mediated by mechanoreceptors. Thus Baust et al. reported that raising the blood pressure may directly cause desynchronization of the EEG in the *encephaleisole* cat, by virtue of its effect on the mesencephalic reticular formation. The mechanical effect of a rise in blood pressure may cause the firing rate of single posterior hypothalamic and mesencephalic reticular neurons to increase. One might well ask, therefore, if this mechanical stimulus also causes the release of humoral substances (for example, vasopressin).

Central Control of the Vasomotor Center

In the cerebral cortex, for example, there are widely distributed points which, on stimulation, modify the blood pressure and which may be way stations in complex circuits of which the medullary and spinal centers are a part.

Stimulation of the gyrus poreus and the sigmoid gyrus in cats and the motor strip in monkeys increases the blood pressure. In addition, when the sensorimotor cortex of the cat is stimulated changes in renal volume occurred without blood-pressure changes, while chronic stimulation of the anterior sigmoid gyrus in cats produced renal vasoconstriction and renal cortical ischemia.

Presumably, these cortical stimuli facilitate vasomotor discharge by

pathways and synaptic connections which largely remain unknown. One of the known outflow tracts from the sigmoid gyrus and the pericruciate cortex is the pyramidal tract. In fact, there is evidence that this tract is involved in the regulation of vasomotor activity, possibly by means of collaterals to the pons and medulla or by influencing spinal autonomic mechanisms directly.

Other cortical areas may produce their effects by other pathways, presumably to the hypothalamus. Lesions of the hypothalamus yielded vasomotor responses to stimulation of the surfaces of the posterior orbital gyrus.

On stimulation of frontal, and temporal cortical structures, pressor and depressor effects occur in many mammals including man. The corticofugal pathways mediating such effects are largely unknown; they are believed not to synapse in the hypothalamus.

On the other hand, the effects of rhinen-cephalic stimulation are most probably transmitted via the hypothalamus. Several rhinen-cephalic areas (the anterior limbic cortex, anterior insula, and the hippocampal gyrus) on stimulation produce changes in blood pressure. The cingulate gyrus, both in man and apes, is involved in blood-pressure regulation. Amygdala stimulation reduces blood pressure. When a number of midline structures—the nonspecific thalamic nuclei and the midbrain reticular system—are subjected

to high-frequency stimulation, marked elevations of blood pressure occur. The effects of such stimulation persist after stimulation stops. Pressor and depressor reflexes may be inhibited by stimulation of the vermis of the cerebellum, presumably by modifying ongoing activity in bulbopontine vasomotor and hypothalamic centers.

The synaptic interactions of these various regions of the brain have not been worked out by intracellular methods. Interactions of the foregoing areas with hypothalamic neurons and with inputs from the mechanoreceptors to the medullary centers may be particularly important in the regulation of blood pressure.

Not only does high-frequency stimulation of the hypothalamus produce acute phasic increases in blood pressure, but the rate of hypothalamic stimulation is linearly related to the impulse frequency in single fibers of the inferior cardiac and the cervical sympathetic nerves. An occlusive interaction between activity produced by baroreceptor activation and hypothalamic stimulation has also been found, while blood-pressure increments produced by stimulation of a peripheral sensory nerve are facilitated by hypothalamic stimulation.

Following the end of simple hypothalamic stimulation, the blood pressure continues to stay elevated for some minutes, possibly due to the

release of vasopressin, and perhaps norepinephrine. Furthermore, varying the frequency of stimulation of a particular hypothalamic site may change a pressor to a depressor response by causing tonic vasoconstrictor discharge to cease. Effects on local changes in blood vessels have also been noted upon stimulating the hypothalamus. In unanesthetized animals blood-pressure increases may be accompanied by expressions of rage when the hypothalamus is stimulated.

From the hypothalamus pathways involved in vasomotor regulation may pass to, or through the mesencephalon. Axons may then travel directly to the spinal cord, or synapse in the tegmentum of the midbrain and the periaqueductal gray matter, or they may travel via the median longitudinal fasciculus to end on medullary neurons. Other descending brainstem pathways, such as the ventrolateral reticulospinal pathway, have also been implicated in vasomotor regulation. Therefore, it seems likely that midbrain reticular formation contributes to cardiac control.

In summary, there is still considerable controversy about the detailed anatomy of supramedullary and suprasegmental outflow from the brain responsible for vasomotor control. From the medulla, excitatory impulses pass to spinal vasomotor neurons in the ventrolateral portion of the spinal cord, while inhibitory influences travel in crossed pathways in the dorsolateral columns.

Spinal and Peripheral Vasomotor Regulation

Stimulation in the medullary pressor area causes bilateral increase in the tonic discharge frequency in the inferior cardiac nerve, and an ipsilateral increment of discharge in cervical sympathetic neurons. Presumably, the inputs from higher centers modify spinal vasomotor reflexes which are released when the spinal cord is cut. Tonic vasoconstrictor discharge still occurs in spinal animals, or in animals in whom the buffer nerves have been cut. Spinal vasomotor neurons continue to be responsive to afferent inputs even after cord transection. Sympathetic pathways extend from the lateral horn of the spinal gray matter to sympathetic paravertebral ganglia. Vasoconstrictor fibers to blood vessels and skin emanate from the thoracolumbar outflow. Their effects are transmitted by postganglionic nerve terminals.

Single unit recordings of pre- and postganglionic sympathetic fibers yield data as to a low rate of transmission and frequency of discharge. The degree of regional vasoconstriction is proportional to the rate of stimulation of the cervical sympathetic trunk. Most significantly, a small change in the rate of stimulation may bring about a marked change in resistance to flow, so that there is a hyperbolic relationship between frequency of stimulation and peripheral resistance.

In most vascular compartments, the narrow range of sympathetic

vasomotor discharge exerts virtually full control over the smooth muscle effector cells. Folkow and Uvnas have suggested that there are regional differences in vasoconstrictor discharge. It is plausible that central autonomic neuronal pools regulating tonic discharge to different vascular regions, may exhibit different excitability levels. Some, while remaining active, may not increase sympathetic discharge in one vascular region but may do so in another. If excitatory drive increases or release from inhibition occurs in neuronal circuits, sudden phasic enhancement of vasoconstrictor discharge may occur in one region and not another.

Neural mechanisms probably exist for massive, phasic increase of vasomotor discharge in appropriate circumstances but also for finely graded differential activity of automatic control over vasoconstrictor tone, due to quantitative differences in excitability levels of neuronal discharge to different parts of the vascular tree.

In addition to the regulation of vasomotor tone by mechanisms outlined above, there are other sympathetic vasodilator mechanisms. Such vasodilator nerves to skeletal muscles of mammals may be regulated by pathways from the motor cortex via the hypothalamus, tectum of the midbrain, and the ventrolateral medulla oblongata, from where they travel to the spinal cord. When stimulated, vasodilation in skeletal muscle is accompanied by constriction in the splanchnic bed and skin. As far as is known this second

system is tonically active. Its outflow runs peripherally to muscle in cats and dogs and possibly to the skin. Little is, as yet, known about the nature of the transmitter substance, or the more intimate neurophysiological properties of this system.

The blood-pressure changes that occur with stimulation of various areas of the brain are, therefore, in part, mediated by the medullary vasomotor center and, in part, by spinal mechanisms to bring about changes in peripheral resistance. Unfortunately, neurophysiologists interested in using blood pressure as their dependent variable do not usually measure changes in cardiac output or resistance to account for the changes in blood pressure. They then fall into the same mistake as many psychophysiologists, which is to measure only a single dependent variable.

Regulation of Respiration: Central Mechanisms

The regulation of rhythmic respiration depends on the alternation of activity of neurons lying in two parts of the pontomedullary respiratory center. The inspiratory center lies in the ventral reticular formation of the upper medulla. Its neurons are driven by the $C0_2$ tension of arterial blood and by input from chemoreceptors to produce an increase in depth of inspiration finally leading to active expiration. The expiratory center lies lateral, dorsal, and rostral to the inspiratory center in the medulla, and has a tonic inhibitory

function on the inspiratory center.

These two centers are the minimal mechanism for the regulation and maintenance of respiratory rhythm. They are profoundly influenced in the intact organism by neural influences coming from more rostral levels.

In the rostral part of the pons lies an inhibitory center, while in the middle and caudal part of the pons a center is found which tonically controls the inspiratory center to prevent respiratory arrest in inspiration with maximal inflation of the lungs.

Several midbrain centers control the lower ones; e.g., stimulation of the posterior hypothalamus produces a paroxysmal increase in respiratory rate. The lateral thalamus reduces the rate of respiration on stimulation. As one would expect, the main cortical sites in mammals from which changes of respiratory rate, depth, and rhythm can be obtained are the temporal, inferior, and superior precentral and orbito-frontal (inhibitory) cortices. This expectation is based on the fact that respiratory patterns can be altered "at will," or in coordination with speaking, singing, laughter, and breath-holding.

From a physiological point of view, normal respiration is regulated by rhythmic periods of inhibition of the tonically active, medullary inspiratory center. This inspiratory tonus is modulated not only by the medullary expiratory center which is progressively excited during inspiration; it begins

to discharge during inspiration to inhibit activity in the inspiratory center. Further control on inspiration is exerted by inhibition of the medullary inspiratory center by the pontine centers so that inspiratory tonus, mediated by the phrenic nerve, is transformed into rhythmic respiration by a series of reciprocally inhibiting interactions amongst brain-stem neurons which regulate respiration.

Of particular interest to psychophysiologists is that the respiration can be markedly influenced by intellectual work which increases its frequency and reduces its amplitude. The type and frequency of respiration may also be changed by exercise and emotional states, such as anticipation, excitement (sexual or otherwise), anxiety, and depressive mood. These states are accompanied by changes in respiratory rhythm. In the hyperventilation syndrome, both the depth and frequency of respiration are enhanced.

Because of the close interaction of psychological factors and respiration, and of respiration and circulation, it becomes incumbent on the psychophysiologist to monitor respiration when measuring cardiovascular variables.

Interaction of Cardiac and Respiratory Function

Rhythmic fluctuations of blood pressure and heart rate are seen in the steady-state in concert with inspiration and expiration. Integration of cardiac

and respiratory function is achieved centrally. The receptor sites are: (1) The pulmonary artery baroreceptors which are particularly sensitive to changes in the rate of pressure with each pulse mainly to adjust respiratory ventilation to changes in venous return; (2) The arterial chemoreceptors which respond to a fall in arterial oxygen tension and/or a rise in the partial pressure of arterial $C0_2$. When stimulated, there is a marked increase in respiration, a reflex fall in heart rate, and a rise in blood pressure, due to an increase in peripheral resistance. There is also vasoconstriction in muscle, skin, viscera, and the kidney, and increased catecholamine production. These responses are mediated, in part, by the hypothalamus; and (3) The lung inflation receptors which respond to stretching of smooth muscle in the lung with inflation to produce a cessation of inspiration. These receptors are also responsible for most of the cardiovascular changes seen during the normal respiratory cycle. Vagal afferent pathways mediate the responses to stretch. Increased pulmonary stretching suppresses the reflex inhibitory effects on the heart when arterial chemoreceptors are stimulated. The central pathways mediating stretching pass both to the bulbar respiratory center and to the hypothalamus and cerebral cortex.

Central Regulation of the Galvanic Skin Resistance

One of the most frequent tools used by psychophysiologists is galvanic skin resistance, or conductance (the reciprocal of resistance). The local

factors which are responsible for conductance or resistance changes most likely have to do with sweating and blood flow through the skin. The more general factors influencing it are psychological stimuli and states.

Removal of the telencephalon, forebrain, and thalamus in cats causes a marked increase in the galvanic skin response, while diencephalic destruction causes it to decline and finally to disappear, suggesting that the telencephalon exerts inhibitory control on the diencephalon in the regulation of the reflex. Yet there is additional evidence that another set of inhibitory influences on the reflex stem from the ventromedial portion of the medullary reticular formation which, when released from facilitatory diencephalic inputs, causes the reflex to disappear. When this caudal set of neurons is cooled or blocked by anesthesia, the reflex is very active. Spinal transection at the level of the first cervical vertebra abolishes the GSR (galvanic skin response).

There is further evidence that there are neuronal mechanisms modulating the bulbar mechanism for GSR regulation in the caudate nucelus and anterior cerebellar lobe.

Central Regulation of Rody Temperature

Two important psychophysiological variables—the moisture of the skin, and respiration—are also involved in heat loss and conservation. Perspiration and panting are processes which cause the body to lose heat.

The hypothalamus is involved in the control of these functions when environmental temperature changes.

Animals, including man, with lesions of the anterolateral hypothalamus cannot regulate their temperature in a warm environment. Body temperature will then rise. When placed in a cold environment, body temperature is maintained because the physiological changes for heat loss fail. In man, heat loss is usually achieved by vasodilatation of the skin, perspiration, and increased respiration.

If lesions are placed in the dorsolateral portion of the posterior hypothalamus, the animal cannot make the necessary physiological adaptations, either to a cold or a hot environment. Why should both forms of adaptation be lost? In all probability, fibers from the anterior (heat loss) hypothalamic nuclei are interrupted by the lesion which also destroys the posterior (heat conservation) mechanisms. The heat conservation mechanisms of the body include epinephrine secretion and shivering to increase heat production, and cutaneous vasoconstriction and piloerection to conserve heat within the body.

Stimulation or local heating of the anterior hypothalamic centers produces sweating, panting, and cutaneous vasodilation and causes core temperature to drop, especially if the environmental temperature is low.

Cold-induced shivering is prevented by anterior hypothalamic stimulation. Yet, when the animal is exposed to cold, the threshold to stimulation is increased.

The two hypothalamic centers seem, therefore, to regulate each other reciprocally. The input to these centers is probably a dual one— one for cold and the other for heat-—from cutaneous thermoreceptors, and from thermoreceptors within the body (especially within the cranial cavity) sensitive to internal changes in temperature.

It follows from this review that it is essential to maintain a constant environmental temperature if one is measuring skin resistance or conductance in psychophysiological experiments.

Central Control of Gastric Secretion

There is evidence to suggest that intracerebral stimulation and lesions of various parts of the nervous system may stimulate or inhibit the secretion of acid and pepsin, or change the production and quality of gastric mucus. For example, low intensity (but long-term) stimulation of the anterior hypothalamus in cats has produced hyperplasia of the gastric mucosa. In dogs, a lesion of the anterior hypothalamus increased the basal acidity of the gastric contents, but did not change the secretory response to maximal histamine stimulation. It may be that the cerebral cortex tonically inhibits

gastric secretion. Both in dogs and in man, decortication raised the basal secretion of acid in the stomach.

These findings are difficult to interpret. Obviously, species differ in their responses to brain stimulation. In addition, the effects of stimulation on the nervous system are always difficult to interpret; partly because different stimulus strengths and frequencies produce different results.

Presumably, the excitatory effects of brain stimulation are mediated by the vagus nerve. But we do not know how these excitatory effects interact with known central inhibitory influences on vagal discharge. An increase in neural activity in the vagus nerve causes an increase in gastric motility and secretion. But the vagus is not purely excitatory; it also mediates inhibitory influences on the physiological activities of the stomach. We still do not now very much about just how these two opposing influences affect the stomach, for example, we do not know how increased vagal discharge can cause a dissociation of acid from pepsin secretion. The kind of information that is needed to resolve this problem is exemplified by the work of Iggo and Leek, who have recorded the action potential from single axons of the vagus nerve of sheep, and related the pattern of discharge from some of these to contractile movements of the stomach.

A dual mechanism for the regulation of gastric acid secretion also seems

to be present in the hypothalamus. Acute increases in gastric acid secretion, as evidenced by a decrease in the pH of gastric juices, can be induced by anterior hypothalamic stimulation. Vagotomy abolishes this response. Stimulation of the posterior hypothalamus produces a delayed increase in gastric acid secretion which reaches its peak after three hours; this response is not mediated by the vagus nerve, but may be mediated by adrenal cortical hormones because bilateral adrenalectomy abolishes it.

Chronic posterior hypothalamic stimulation can produce gastric and duodenal hemorrhage due to ulceration. The increase in gastric acid secretion produced by insulin also seems to act by the medium of the hypothalamus and vagal afferent outflow.

All the mechanisms which produce acid secretion in the stomach are still not known. Vagal afferents to the stomach may control gastrin and pepsinogen secretion. Gastrin is a polypeptide which regulates acid secretion in the stomach, and is, in turn, regulated both by the vagus and by a negative feedback mechanism by increases in the acid content of gastric juice.

The Hypothalamus and Other Psychophysiological Relationships

Sexual Behavior

The autonomic nervous system is clearly involved in the sexual act, both

erection and ejaculation are under its control. In addition, during sexual intercourse changes in heart rate, blood pressure, respiratory rate and depth, vasomotor changes, and sweating have been recorded. Psychological factors are presumed to play a considerable role in determining the range and extent of such changes, and the responsiveness of the subject during sexual intercourse.

Very much less is known about the role of the autonomic nervous system in sexual behavior other than sexual reproduction. However, it is known that in mammals the posterior hypothalamus plays a part in sexual behavior and oestrus.

In fact, most of the work on sexual behavior has focused on its hormonal control. The hypothalamus is also involved in patterned emotional behaviors —such as the "defense reaction"—which always has very marked concomitants of autonomic arousal. Involved in these patterns is the complex relationship between the limbic input to hypothalamic activity.

The hypothalamus also plays a role in behavioral states such as sleep and wakefulness, in immune responses, in stress reactions, in the prevention of pulmonary edema, in eating behavior, in aggressive behavior, and in the control of the secretion of pituitary trophic hormones. The implication of the autonomic nervous system in these responses remains to be elucidated.

Other Psychophysiological Phenomena

Psychophysiologists also measure electrical phenomena, such as the electroencephalogram (EEG), "evoked" potentials (EP), the "contingent negative variation" potential (CNV), and the electromyogram (EMG).

Despite the fact that it is over forty years since the EEG was first described, we still do not know what aspects of neuronal or other neural functioning it reflects. It is used to measure differences of activity in behavioral steady-states such as sleep and quiet wakefulness, delirium and coma. It is affected in its activity by drugs, mental activity, sensory input, and by changes in the blood pressure, etc.

Evoked potentials (EP) can be recorded from the scalp following stimulation of receptors—such as in the eye, ear, or skin—by means of special computer techniques which accumulate time-locked signals. Much controversy has surrounded the EP, because in the intact subject time-locked scalp muscle potentials must be differentiated from a signal of cerebral origin. EP's reflect the activity of sensory receiving areas to incoming impulses in specific sensory tracts produced by the stimulus. The early waves of the EP are believed to consist of activity in thalamocortical projections, the arrival of impulses in cortical neurons and their responses to them. No one knows what central processes the later waves represent. In fact, the mechanism of EP wave forms has resisted analysis to date.

A special form of EP is the CNV, a slow negative D.C. wave recorded from the forehead which is produced when a subject attends to a task. It again must be differentiated from muscle EMG activity such as produced by blinking of the eyes.

General speaking, EP and CNV are influenced mainly by central states—such as variations in attention, sleep, drugs, etc. However, it should be noted that in animals, at least, the early components of the EP are largest in deep barbiturate narcosis.

The EMG's are usually recorded from the skin surface by means of special electrodes, and reflect tonic and phasic changes in tension in large numbers of muscle fibers. They are particularly useful in demonstrating changes in eye, neck, or submental muscle tone during sleep stages. Eye movements are present and tonic submental activity is minimal during REM period sleep. Muscle tension is increased during apprehensive or alerted states.

The regulation of muscle tone is not fully understood. It is reflexly maintained by segmental mechanisms, and regulated by two sets of afferent input. Inhibitory and excitatory influences play upon the alpha-motoneuron through the mediation of the inhibitory Renshaw cell of the cord, and by descending pyramidal, vestibulospinal, rubrospinal, reticulospinal, and other

pathways.

Further Integrative Mechanisms

The Relationship Between the Autonomic and Endocrine System

Many of the problems in inference and interpretation about the results of psychophysiological experiments would be simplified if multiple rather than single physiological variables were measured. This would allow the psychophysiologist to obtain a broader view of the biology of responses to the independent variables which he has chosen for his experiment.

For it is increasingly apparent that there are very important interactions between central and peripheral autonomically mediated responses and the endocrine system, and, therefore, metabolic processes. What is more, the interactions between these systems occur in both directions. We have seen that ACTH (adrenocorticotrophic hormone) by increasing cortisol production in the adrenal cortex, induces PNMT which, in turn, catalyzes the biosynthesis of epinephrine from norepinephrine. Epinephrine, in turn, mobilizes liver glycogen, through the medium of cyclic AMP (adenosine monophosphate) to increase blood sugar. Insulin increases gastric secretion reflexly through the vagus nerve. Mechanoreceptors in the great blood vessels reflexly and, in part, regulate the release of the mineralo-

corticoid, aldosterone, which plays a central role in the control of electrolyte metabolism and hence body water, and at the same time regulate catecholamine and ADH release. Sympathetic discharge can bring about renin release from the kidney, hence angiotensin production, and thereby influence the blood pressure. Angiotensin II may increase the firing rate of supraoptic neurons, and hence increase the release of antidiuretic hormone, thereby diminishing urine production. Angiotensin II may also influence CNS mechanisms directly to increase the blood pressure. The sympathetic nervous system mediates the light-induced regulation of melatonin which, in turn, at least, and in some mammals, influences oestrus behavior.

The central integration of autonomic outflow, as well as many metabolic processes, occurs in the hypothalamus. The control and regulation of the pituitary trophic hormones is carried out by hypothalamic cells. These are believed to “transduce” electrical impulses into chemical substances, by the release of biogenic amine neurotransmitters which, in turn, control the release of corticotrophin, follicle-stimulating and thyrotrophin releasing and other factors. Posterior pituitary hormones such as ADH are particularly sensitive to environmental and other (such as painful) stimuli through the medium of the anterior hypothalamus and the hypothalamico-neurohypophysial tract.

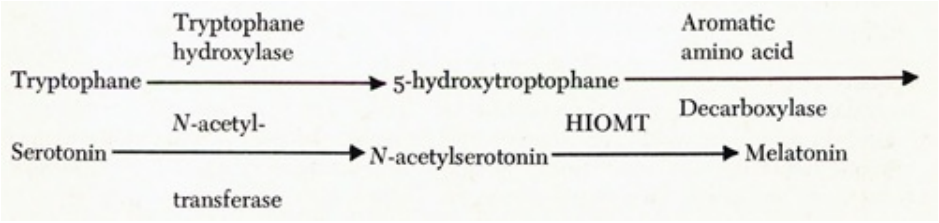
Generally speaking, responses to rapid and short-term environmental

changes are mediated neurally by the autonomic nervous system by means of ganglionic relays and postganglionic terminals to release neurotransmitter substances at local sites. Physiological adaptations to slowly changing or long-term environmental stimuli or situations are carried out both by neuronal and hormonal agents. These hormones act “at a distance” and often at widespread sites. The release of each hormone has its own time course as discussed in Chapter 24. Intermittent and repeated environmental changes may bring about eventual physiological adaptation. When repeated or continuous environmental factors are imposed on young animals, their physiological responses later in life are determined by the earlier experience, thus providing a basis for our understanding of a critical problem in all psychophysiological research, i.e., that of individual differences in response tendencies.

A special and very interesting interaction between the autonomic nervous system, behavior, and hormones has been worked out in the pineal gland.

Fiske et al. had shown that the weight of the pineal gland decreases when rats are kept in continuous light. Under such lighting conditions female rats remain in continuous vaginal oestrus. These, and the observation that extracts of the pineal gland of cattle inhibits oestrus, led to the observation that melatonin reduces the incidence of oestrus in the rat.

We owe to Axelrod and his group the elucidation of the biosynthetic pathway of melatonin from tryptophane:



Wurtman, Axelrod, and Phillips showed that levels of hydroxyindole-O-methyltrans-ferase (HIOMT) in the pineal gland are elevated when rats are kept in continuous light. Therefore, light reduces the synthesis and release of melatonin, and this would explain why continuous light produces persistent oestrus.

Axelrod and his associates have worked out the rather complex and indirect pathway from retina to pineal and the manner in which the biosynthetic machinery of the gland is influenced:

Environmental light in the mammal passes via the retina → inferior accessory optic tract → medial forebrain bundle to the medial terminal nucleus of the accessory optic system → preganglionic sympathetic fibers of the spinal cord → the superior cervical ganglion from which postganglionic fibers pass upward to the parenchymal cells of the pineal gland whose terminal release norepinephrine.

At the same time light clearly also stimulates the retina to entrain impulses which pass via the classical visual pathways to the visual cortex, and in an as yet mysterious way to produce the experience of discriminated light.

The release of noradrenaline in the pineal gland influences the formation of melatonin from tryptophane by inducing the enzyme, *N*-acetyltransferase (which converts serotonin into *N*-acetylserotonin).

Two further points about the regulation in the pineal gland need, however, to be made. One highlights the importance of taking into account the time during a biological rhythm, and, the second, the importance of the age of the animal, at which an experiment is done.

The first case is illustrated by the fact that there is a biological rhythm for the content of serotonin in the pineal—one of the important precursors of melatonin—and for norepinephrine in the pineal gland. The content is high during the day under normal lighting conditions, and low at 11:00 p.m. This rhythm is endogenous, although its driving oscillator is unknown. Despite its endogenous nature, the oscillator can be entrained by light, e.g., when day and night are reversed experimentally.

Norepinephrine content, on the other hand, which reaches its highest levels at night is not controlled by an endogenous oscillator but is under the direct environmental control of light. Thus, its high nocturnal content

corresponds to the high nocturnal content of HIOMT, and, therefore, of melatonin synthesis.

It is, however, of great interest that the oscillator for serotonin is not operative until the rat is six days old. Furthermore, in young rats before they are twenty-seven days old. light affects the serotonin level in the pineal gland by an extraretinal pathway; after this age this earlier pathway is no longer operative.

Integrative Function of the Autonomic Nervous System

Certain generalizations about the overall function of the ANS in maintaining homeostasis have beclouded the fact that sympathectomized animals do survive and lead quite a normal existence. They eat, grow, sleep, and reproduce in the laboratory. They may not be able to suckle their young, and may be unduly cold-sensitive. Only under conditions of stress do responses fail but even then stresses must be quite severe (such as asphyxia stress) to reveal the absence of sympathetic regulatory devices. In other words, there seem to be adaptations to the absence of the sympathetic nervous system, in which otherwise redundant mechanisms take over its function.

Modern Concepts

Modern concepts about the autonomic nervous system no longer tend to focus as much on its role in maintaining the "constancy of the internal environment." Rather, its role is seen as one of the three main mediators of the organism's responses to his natural or social environment.

This view is implicit in Walter Cannon's work but in retrospect it is a point of view that has been underplayed. Rather, the field of psychophysiology has moved in the direction of the study of controllable psychological and sociological variables in the laboratory while measuring single physiological ones. Furthermore, such studies deal only with responses in the acute experimental situation. We know very much less about the autonomically mediated responses to chronic "stresses."

The study of organismic responses, that is, the integrated psychological and a broad range of physiological responses, to everyday, naturally occurring situations requires different methodologies. The responses obtained by new techniques may require further analysis in the laboratory.

However, a giant step has been taken in this direction by the research performed in the laboratories of Axelrod, Henry, and Kopin. They have combined a number of techniques, taken from such diverse fields as ethology, experimental psychology, biochemical pharmacology, and enzymology, to demonstrate the effects on animals of short-term and long-term exposure to

stress and how such exposure affects mediating autonomic mechanisms.

Very acute stresses, preparation for activity and novel experiences, are now known to be divided into anticipatory and reactive phases, and are associated with increases in systolic blood pressure, heart rate, and catecholamine and steroid excretion, etc. In all likelihood these changes are largely mediated neuronally. The mechanism underlying the increase in catecholamines, especially norepinephrine secretion, appears to be due to a sharp increase in norepinephrine synthesis from tyrosine but not dopa, when an increase in sympathetic nerve activity occurs. However, no increase in tyrosine hydroxylase activity occurs, so that either no new enzyme is formed or formation is inhibited by norepinephrine.

The absence of change in tyrosine hydroxylase content of tissue during acute stresses or stimulation stands in contrast to the change that is produced by sustained stress or sympathetic nerve activity.

Thoenen, Mueller, and Axelrod have shown that a reflex increase in sympathetic nerve activity over several days produced a marked increase in TH activity in the adrenal gland and in the superior cervical ganglion of the rat, and in the brain stem of the rabbit. The activity of PNMT is also increased. By a number of experimental procedures Axelrod and his co-workers have shown that the changes in content of these enzymes in the adrenal gland and

in the superior cervical ganglion are not only neuronally mediated but depend on the formation of new protein. In other words, they have shown that the increase in TH activity is transsynaptically induced.

The increase of PNMT produced by neuronal activity is, however, also under the control of ACTH. It depends on new protein (enzyme) synthesis and occurs even in hypophysectomy and the administration of ACTH. To a much lesser degree, the two other biosynthetic enzymes, TH and dopamine hydroxylase, are similarly controlled.

That these changes in enzyme activity with sustained neuronal activity are not only the product of the laboratory is attested to by the exquisite work of Henry and his co-workers. It confirms the fact that chronic stress produces marked changes in the biosynthetic enzymes of norepinephrine, but, in addition, it produces correlated changes in blood pressure and renal pathology.

The results of this research have been confirmed by the use of the restraint technique. Further evidence for the dually mediated changes in adrenal enzyme content has been obtained. Other work, using this method, provides insight into some of the possible brain mechanisms mediating these changes.

Restraint-immobilization has potent effects on the peripheral and

central content of biogenic amines. Kvetnansky and Mikulaj have shown that in rats immobilization for ninety minutes produces an increased excretion level of norepinephrine and epinephrine, associated with a decrease in adrenal epinephrine (but not norepinephrine) content which persisted for twenty-four hours after its conclusion. With persistent immobilization, adrenal epinephrine content was unaffected, but norepinephrine content increased, while the urinary excretion of epinephrine remained increased. These results suggest that the adrenal medulla enhances its ability to replace released epinephrine with repeated immobilization stress. This "adaptation" to stress appears to be due to a neuronally dependent elevation of TH and PNMT in the adrenal medulla. When immobilization is stopped, TH levels diminish with a half-life of about three days.

Following the end of immobilization there is a latency period of about six hours for levels of TH and PNMT to become elevated. Further elevations of levels occur in the next seven days of immobilization, but after six weeks of daily immobilization, no further increases occur.

The long-term increase in catecholamine levels in the adrenal medulla produced by immobilization are not only neuronally dependent but are *also* under the control of ACTH. After hypophysectomy, depletion levels with restraint are greater than in control animals, and levels of TH and PNMT fall. On repeated immobilization, TH levels but not PNMT in hypophysectomized

rats do, however, rise but never to control levels. The use of TH levels in operated rats is neuronally dependent in the main, whilst the rise in PNMT, and some of the rise in TH levels, depends almost entirely on ACTH administered prior to the stress.

On the other hand, serum dopamine-*β*-hydroxylase (which transforms dopamine into norepinephrine) was increased after one thirty-minute immobilization of rats, and continues to increase with daily immobilization for a week. The source of this increase is not, however, the adrenal gland but sympathetic nerves.

Immobilization stress of three hours also significantly accelerates the disappearance of radioactive norepinephrine from heart and kidney. The question of how immobilization stress is centrally translated into these neuronally and hormonally dependent peripheral changes is unanswered except for some very interesting work by the Welches. They showed that restraint stress can cause a greater elevation of *brain* norepinephrine and serotonin in mice who previously had spent eight to twelve weeks in isolation, when compared to littermates housed in groups.

This elevation of brain amines occurs despite the fact that the isolated mice have slower baseline turnover of brain biogenic amines than those housed with others.

This work has several important implications. The isolated mice were behaviorally more hyperexcitable than the housed controls. In other words, previous experience affected behavioral response tendencies, while the finding of different turnover rates and greater elevations with immobilization clearly indicates that previous experience may lead to individual differences in brain biogenic amines as well as behavior.

This work further points up the contention brought forth in this chapter that autonomic and endocrine mechanisms are closely interrelated and interacting. The full range of these interractions and mutually regulating mechanisms is still to be worked out.

Finally, psychophysiology brings us face to face with a major scientific and philosophic issue. Which are the means by which psychological responses —thoughts, feelings, their awareness, etc.—are translated, if indeed they directly are, into autonomically mediated responses? In other words—the mind-body problem. There is no answer to this question, and therefore, much of the meaning of psychophysiological correlations and concomitances remains obscure, meaningless, or without significance.

Technical Aspects

In addition to having mastered a number of skills, psychophysiologists must have considerable expertise in instrumentation. Special attention must

be given to make their instruments reliable and valid: For example, special instruments have been devised for measuring blood pressure in intact subjects.

All the techniques which have been devised require some knowledge of electronic recording devices. For the technical aspects of psychophysiology, the reader is referred to the *Manual of Psychophysiological Methods.*

Concluding Remarks

The data and concepts reviewed in this chapter are mainly derived from acute experiments performed on anesthetized animals. In addition, these experiments tend to have as their purpose the study of a single dependent autonomic variable, while varying an independent other variable. Such analytic experiments tend to obscure the complex, integrated adjustments that occur in autonomic function in intact, free-ranging animals, and to obscure patterns of autonomic change brought about by changes in the animal's environment. There is some evidence that patterned autonomic changes (and behavioral changes) may be quite specific to particular situations. They may be different in an animal anticipating avoidance conditioning than they are in anticipation of muscular exercise. Or, they may be different in an animal anticipating a fight with another, than during the actual engagement.

Yet, any understanding of autonomic functioning must be based on knowledge of the intrinsic mechanisms which underlie them. For this reason these mechanisms have been reviewed. In Chapter 23, Hofer will review the principles which govern autonomic psycho-physiological relationships in the natural life of man and animals. These relationships have been studied in the laboratory or field in intact animals. The data derived from these studies reveal a different level of organization of autonomic functioning than an analytic experiment can do.

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Notes

1 Even the EEG may be influenced by changes in cardiovascular dynamics.

2 Acetylcholine is, of course, the transmitter substance at all neuromuscular junctions involving skeletal muscle and may play a role in neurotransmission in the CNS.

3 Aldosterone is the principal steroid, produced by the adrenal cortex, regulating body salt.