Journal of Pharmaceutical Sciences

AUGUST 1972
VOLUME 61 NUMBER 8

REVIEW ARTICLE

Physiological Effects of Environmental Stimuli

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Keyphrases ☐ Physiological effects of environmental stimuli—review ☐ Environmental stimuli—physiological effects, review ☐ Stress reaction—relationship to environmental stimuli ☐ High altitude stress—effects of decompression and hypoxia ☐ Disease—as related to stress, environmental stimuli ☐ Environmental pharmacology—interaction of drugs and environment ☐ Pharmacology, environmental—interaction of drugs and environment

The physiological, biochemical, and behavioral effects of environmental stressors on the living organism have been under intensive investigation for over 3 decades. Since Selye (1) first described the syndrome produced by various noxious agents in 1936, investigators have identified biochemical, physiological, and pathological changes produced by nonspecific stress. Barry and Buckley (2) published a comprehensive review on drug effects on animal performance and the stress syndrome in 1966; therefore, this present review is restricted mainly to the more recent literature.

Stress *per se* appears to be a contributing factor to the development of diseases of the cardiovascular system, CNS, and GI system as well as other chronic diseases. Physiological and endocrinological changes induced by environmental factors may alter drug activity markedly *via* physiological and/or biochemical changes, and chemicals may alter the response of the organism to its environment (3). In addition, environmental stimuli may alter drug metabolism as well as the absorption, distribution, and excretion of drugs. The time course relationship of biochemical, endocrinological, and physiological changes occurring during prolonged periods of stress exposure may be related to the development of specific pathological conditions and give us a better understanding of the disease pattern and perhaps a better rationale for the treatment of the disease (3). The public is presently concerned with environmental factors that could in certain cases be called environmental pollutants. For example, Leake (4) recently defined noise as both a pollutant and a stressor. Changes in environmental conditions such as temperature, hypoxia, working conditions, and even traffic may produce marked psychological and endocrinological changes within the living organism.

The purpose of this present report is to review the more recent data in an attempt to correlate the effects produced when living organisms are exposed to conditions that produce anxiety and other emotional reactions and the development of certain chronic diseases, as well as the time course relationship of biochemical, endocrinological, and physiological changes that may be related to the development of these diseases. The possible alterations in drug action by environmental stimuli and the alteration of the response of the organism to his environment by drugs are of utmost importance and have opened a new facet in pharmacology which could be called "environmental pharmacology."

ENVIRONMENTAL STIMULI AND THE STRESS REACTION

Selye (1, 5–7) stated that the living organism subjected to alarming stimuli passes through three stages, which he termed the general adaptation syndrome (GAS). The three stages [(*a*) the alarm reaction, (*b*) the stage of

resistance, and (*c*) the stage of exhaustion] have been described in detail (1, 2, 5–7) and discussed in the hundreds of publications by Selye and his coworkers which are too numerous to list in this review. This response of the living organism to "nonspecific stressors" is well documented; however, it is still not universally accepted. Mason (8) strongly suggested that there should be a reevaluation of the concept of "nonspecificity" in the stress theory, especially since some findings have emerged from the study of endocrine regulation which have important implications concerning the validity of the stress theory in general and the concept of nonspecificity in particular. He further reported that in initial attempts to study the endocrine responses to such stimuli as exercise, fasting, heat, and cold, his group was struck by the fact that it was extremely difficult to isolate these stimuli in the laboratory situation from their natural psychological concomitants. He suggested that the "primary mediator" underlying the pituitary–adrenal cortical response to the diverse stressors of earlier stress research may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole.

Adrenergic Component—Rats subjected to chronic, intermittent exposure to variable environmental stressors (noise, lights, and motion) showed a significant increase in the rate of turnover of norepinephrine in the brain during the first 4 weeks of exposure to the stressors (9, 10). These investigators administered α-methyltyrosine, 100 mg./kg. p.o., to inhibit tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis, and reported a 40–50% depletion of brain norepinephrine in the nonstressed treated group whereas more than 80% of brain norepinephrine was depleted in the stressed treated group during this same time period. However, by the end of the 6th week and to the termination of the study at the 14th week, the percent depletion of norepinephrine was not significantly different between the α-methyltyrosine-treated stressed and unstressed groups. α-Methyltyrosine treatment also was capable of preventing the development of hypertension in the stressed animals; the blood pressure of the untreated stressed group rose progressively to a mean systolic blood pressure of 151 mm. Hg by the 10th week of stress exposure whereas the mean blood pressure of the α-methyltyrosine-treated rats at this time period was 108 mm. Hg. Electroshock stress caused an acceleration of the disappearance of ^{3}H-norepinephrine, suggesting an increase in norepinephrine turnover in the peripheral adrenergic system (11).

Welch and Welch (12) found that exposure of Swiss mice to natural stimuli failed to accelerate brain catecholamine depletion after the inhibition of biosynthesis with α-methyltyrosine. However, the natural stimuli consisted of either isolation stress or crowding and, therefore, appear to be less severe than that used by investigators reporting increased turnover (9–11). Rubenson (11) found that cold stress produced a decrease in the tritiated norepinephrine content of the heart and skin but not of striated muscle, kidney, or spleen and that immobilization stress increased the turnover of norepinephrine from the heart and kidney but not from the spleen and striated muscle. Therefore, it would appear that the degree of the environmental stimuli and the time of exposure to the stimuli are of utmost importance in their overall effects on central and peripheral adrenergic activity. Humans subjected to three 2-hr. periods of the distracting criticisms, noise, and lights showed an increase in systolic blood pressure and in the urinary excretion of norepinephrine and epinephrine indicative of an increased sympatho-adrenomedullary activity induced by this simulated work situation (13) which also results in increased plasma triglyceride levels. It has been suggested that the plasma triglyceride concentration is in direct relationship with the fat-mobilizing capacity of the individual which, in turn, is determined by the level of sympathetic activity (14). Free fatty acid levels in the circulating blood increased in humans who, under hypnotic state, were given anxiety-provoking suggestions (15). The data obtained by these investigators suggest that the free fatty acid pool increase was due to a primary rise in free fatty acid production, which could be inhibited through the use of the β-adrenergic blocking drug, propranolol.

A large number of studies have recently been undertaken to investigate the physiological effects of noxious sounds or noise. High pitched sounds (10–20 kHz.) produced a release of the antidiuretic hormone and epinephrine in the rat (16). Exposure of normal human subjects and cardiocirculatory and psychotic patients to sound (2000 Hz.) for 30 min. at an intensity of 90 db. caused increased activity of adrenal cortical and adrenergic functions (17). Patients with chronic myocardial infarctions had a higher level of urinary excretion of norepinephrine than the other two groups, suggesting that cardiac infarction patients react to audiogenic stress with increased release of norepinephrine because of a more active aggressive psychological personality. In addition, systolic and diastolic pressure rose significantly in many labile hypertensive patients exposed to noise, correlating with increased catecholamine excretion. The same authors found that some schizophrenic patients exposed to noise showed very high levels of urinary norepinephrine even under chlorpromazine treatment and that these high excretion rates of norepinephrine were similar to excretion rates obtained in psychotics during extreme aggressive episodes.

The response of living organisms to heat and cold stress differ somewhat from that obtained with other types of stressors. Leduc (18) showed that there was an increase in the urinary excretion levels of catecholamines during exposure of animals to cold, suggesting an increase in activity of the sympatho-adrenal system. Disulfiram, an inhibitor of dopamine β-hydroxylase, decreased cardiac norepinephrine levels to a greater extent in animals kept at 2° than in animals kept at room temperature, suggesting an increase in cardiac norepinephrine utilization during "exposure" (19). The norepinephrine levels in the brain were significantly lower in animals kept at both room temperature and at 2° following disulfiram administration, probably due to a rapid turnover of norepinephrine in the CNS. Disulfiram, on the other hand, produced an increase in brain dopamine, which was even slightly more pro-

nounced in the animals exposed to cold. These data differ from those reported for rats subjected to intermittent noxious stimuli; the stressed rats treated with α-methyltyrosine showed a marked decrease in brain norepinephrine when compared to treated nonstressed and untreated stressed animals, whereas there was no difference in the dopamine levels between the treated stressed and unstressed animals (9).

Spector (20) found that rats exposed to either cold-room environment (4°) or to exercise showed no significant difference in the endogenous content of tissue norepinephrine as compared to unstressed animals. However, after the administration of α-methyltyrosine the animals subjected to the stress exhibited a significantly greater reduction of the tissue norepinephrine levels, suggesting a greater utilization of the catecholamine stores and an increased rate of synthesis during stress. Long-term exposure of mice (18) and repeated short exposures of mice (21) to cold produced an adaptation of the animals to the cold environment. However, the long-term adaptation to cold resulted in increased sensitivity to norepinephrine, whereas short-term adaptation did not produce this change in norepinephrine sensitivity. Therefore, although both types of adaptation led to increased survival at very low temperatures, it appears that the mechanisms involved are different. Cold exposure resulted in a time-dependent increase in tyrosine hydroxylase activity in the adrenals and superior cervical ganglion (22); however, the increase in tyrosine hydroxylase activity in the CNS was restricted to the medulla oblongata. Although other investigators (23) showed that the highest increase in catecholamine synthesis following cold exposure occurred in the hypothalamus, most of the cell bodies supplying the hypothalamus with adrenergic fibers are located in the medulla oblongata (24) and the main site of enzyme synthesis is the cell body. The studies of Thoenen (22) suggest that the increased utilization of norepinephrine following cold exposure is not only compensated for by an immediate, short-term adaptation to the increased needs of transmitter production but also by a long-term adaptation involving induction of tyrosine hydroxylase.

Norepinephrine released from peripheral sympathetic neurons appeared to function as the mediator for nonshivering thermogenesis in animals subjected to prolonged cold exposure (25). Rats treated with decaborane, a compound that markedly decreases the norepinephrine content of the heart, spleen, and liver (26, 27), died within 4–6 days when exposed to 3°, but all of the control animals survived (26). Since these animals increased their daily urinary excretion of epinephrine to amounts equivalent to the entire epinephrine content of the adrenal glands, the results suggest that epinephrine cannot fully protect the animals from cold stress. Decaborane-treated adrenalectomized rats exposed to 3° died in less than 20 hr., whereas all of the adrenalectomized-control animals survived this temperature. The oxygen consumption of the rats at 4° increased by approximately 80% within 30 min. (28).

The basal metabolism and the plasma free fatty acid and glucose levels of chemically sympathectomized animals at room temperature were approximately normal (29); however, on exposure to cold they could neither conserve heat nor generate additional heat. Unlike animals having intact sympathetic systems, they demonstrated vasoconstriction, piloerection, and shivering, and body temperature rapidly declined. These animals also failed to produce the expected increases in plasma free fatty acids and glucose, but there was an increase in plasma corticosterone. Chemically sympathectomized rats pretreated with epinephrine prior to cold exposure did show increased plasma levels of free fatty acids and glucose but also exhibited piloerection, vasoconstriction, and shivering. These studies (29) indicate that the sympathetic nervous system is absolutely essential for the mammalian organism to maintain thermal homeostasis when exposed to low temperatures. Data from these studies also suggest that the emergency mobilization of a vital source of stored energy, the triglycerides in fat depots, is under the direct control of norepinephrine released from sympathetic neurons and that epinephrine from the adrenal medulla is not needed for this function. There was a similarity in responses in adrenalectomized and chemically sympathectomized rats exposed to cold; however, the effects of adrenalectomy could be reversed by the administration of cortisone but not by epinephrine.

The inability of adrenalectomized rats to survive in cold could also be reversed by other glucocorticoids such as dexamethasone and prednisolone or by chronic treatment with aldosterone (30). These treatments restored the responsiveness to catecholamines, suggesting that: (*a*) the adrenalectomized rat may be considered as a functionally sympathectomized animal because of impaired responsiveness of effector systems which normally are activated by sympathetic function, and (*b*) the abilities of the animals to vasoconstrict, piloerect, shiver, and mobilize glucose and free fatty acids are restored by the steroids. Rats exposed to an environment of approximately 5° for 2–7 weeks showed a significant decrease in both serum glucose and serum insulin concentrations (30). Since both epinephrine and norepinephrine inhibit the release of insulin, the cold-exposed animal should exhibit these lower blood insulin levels.

Studies using the dopa-decarboxylase inhibitor *N*-(DL-seryl)-*N'*-(2,3,4-trihydroxybenzyl)hydrazine (RO 4-4602) in rats subjected to cold stress showed that the treated rats excreted less norepinephrine in the cold environment than did the controls; however, this diminished norepinephrine excretion was accompanied by an increased urinary epinephrine excretion (32). These data correlate well with the conclusion of Leduc (18) that, although norepinephrine is the main mediator in the chemical regulation of heat production, any condition that diminishes the secretion of norepinephrine elicits a compensatory increase in epinephrine release. Metaraminol administration (1 mg./kg. i.p.) 2 hr. prior to exposing rats to 4° depressed the cold-induced increase in norepinephrine excretion which was accompanied by a compensatory increase in epinephrine release, which presumably aided in the maintenance of normal thermia (33).

Anterior Pituitary–Adrenocortical System—Rats exposed to intermittent neurogenic stimuli for prolonged periods demonstrated a threefold increase in serum corticosterone levels from Weeks 1 through 4 (9, 10). The data suggest that the response of the living organism to prolonged periods of intermittent exposure to environmental stressors appears to be divided into two distinct phases:

1. The acute phase which involves stimulation of central adrenergic neuronal centers and concomitant liberation of ACTH from the anterior pituitary, resulting in elevation of adrenal steroid secretion.

2. The chronic phase which is associated with a reduction in cortical steroid secretion and central sympathetic nervous activity to prestress levels.

The activation of central sympathetic centers and the concomitant stimulation of the anterior pituitary–adrenocortical axis are important in the initial phase of the stress response, and these two components are temporally, if not causally, related. Smelik (34), in discussing the regulation of ACTH secretion, hypothesized that the stress response is initiated by activation of the hypothalamic centers through afferents from the rhinencephalic or mesencephalic limbic systems and that the posterior and anterior regions of the hypothalamus, respectively, mediate the subsequent phase of the neuro-endocrine emergency response. There is an increase in the ACTH-releasing hormone (CRF) in blood of rats subjected to the stress of noise stimuli (35). In addition, other stressful stimuli such as tension on the vagus nerve, surgical procedures under ether anesthesia, and hypovolemia also produce an increase in corticotropin-releasing factor. Although there are marked diurnal variations in plasma corticosterone levels, the changes observed in these levels in adult female rats subjected to 3-min. ether or immobilization stress did not differ (36). That is, despite the marked differences between morning (trough) and afternoon (peak) nonstress levels, similar stress-induced increments in concentrations of plasma corticosterone were observed. These data suggest that the acute plasma corticosterone responses to certain types of stressors are independent of endogenous variation in nonstress levels of this steroid in the female rat.

There is also evidence of a circadian rhythm in hypothalamic corticotropin-releasing factor activity (37, 38). The peak value of corticotropin-releasing factor activity occurred at 6:30 p.m. and the minimum at 8:30 a.m. using a 13-hr. light cycle and an 11-hr. dark cycle beginning at 6:00 a.m. (38). These highs and lows are similar to those reported for corticosterone levels. Although circadian rhythm of corticotropin-releasing factor activity became evident between the 14th and 21st days of postnatal life, the responsiveness of stress was evident as early as the 7th day (stress consisted of exposure to ether vapor for 1 min. followed by laparotomy) (39). These investigators concluded that the slow maturation of synthesis or release of hypothalamic corticotropin-releasing factor may account for the "stress-nonresponsive period" during the early postnatal days in the rat.

There appears to be complete agreement that the pituitary–adrenal axis is activated during acute stages of stress. Immobilization stress increases the levels of both the adrenal and plasma corticosterone (40, 41). The possible role of adenyl cyclic adenosine monophosphate (AMP) in the response to immobilization stress was also investigated (42). Rats subjected to varying periods of immobilization showed a maximum increase in cyclic adenosine monophosphate levels in the whole adrenal gland in approximately 30 min., with the levels returning to baseline by 150 min. of immobilization. Pretreatment with theophylline, a phosphodiesterase inhibitor, decreased the onset of maximum levels of cyclic adenosine monophosphate in the adrenals to 10 min. of immobilization. Although these investigators found that the splanchnic nerve innervating the cortex exerts a synergistic influence on changes in cyclic adenosine monophosphate induced by pituitary factors, the data suggest that ACTH is mainly responsible for the increase in adrenal-cortical cyclic adenosine monophosphate.

The role of central adrenergic activity in the control of ACTH release from the anterior pituitary induced by stress has been studied in several laboratories. A marked reduction in brain catecholamines produced by α-methyltyrosine or reserpine did not significantly affect the activation of the anterior pituitary–adrenocortical axis induced by a variety of stressors (43). Stimulation of ACTH release by reserpine was not related to the ability of this drug to release or deplete brain catecholamines (44, 45). Although these reports indicate a lack of causal relationship between brain amine release and pituitary–adrenocortical activation, the stressful procedures utilized in these studies were severe and of short duration. These data may not be completely relevant to those responses obtained in animals subjected to prolonged stressful situations in which there appears to be a definite temporal relationship between activation of central sympathetic centers and stimulation of the anterior pituitary–adrenocortical axis (9, 10). These latter studies exposed rats to 4 hr. of variable stressors that were composed of visual, audiogenic, and motion stimuli 3 days/week on a 6-day/week randomized schedule.

The effects of each of these individual stressors on serum and adrenal corticosterone levels and *in vitro* adrenal corticosterone synthesis rates were recently investigated[1]. Prior to the first exposure but immediately following handling, the serum corticosterone levels were 30 mcg./100 ml., which in controls fell to 15 mcg./ml. after 90 min. and to 10 mcg./100 ml. at 3 hr. Exposure to audiogenic (100 db. for 30 sec. each 5 min.) or visual (150-w. spotlights for 30 sec. of each minute) stimuli produced serum corticosterone levels that were not significantly different than controls. However, motion (140 oscillations/min.) produced an elevated serum corticosterone level (51 mcg./100 ml.) in 30 min. which peaked (60 mcg./100 ml.) at 1 hr., declining slowly to 42 mcg./100 ml. following 4 hr. of exposure to the stressor. Changes in adrenal corticosterone and corticosterone synthesis rates *in vitro* paralleled those in

[1] R. J. Ertel, T. Shih, and H. H. Smookler, unpublished data.

serum corticosterone. Therefore, it appears that motion, as a noxious stimulus, represents the most severe of these three environmental stressors and that chronic exposure produces changes in the sensitivity of the pituitary–adrenocortical axis[1].

Investigators have shown that serotonin stimulates ACTH secretion when administered parenterally to animals (46–48). There was an increase in the turnover time of brain serotonin of approximately 57% in isolated compared with grouped mice (49). Since the mice invariably became aggressive after 4 weeks of isolation, the changes observed in brain serotonin turnover suggested possible correlations between behavioral changes and central metabolism of serotonin. Studies undertaken to investigate the effect of variations in brain serotonin level on the reactivity of the anterior pituitary–adrenocortical system to stress suggested that the changes in the whole brain serotonin level *per se* do not affect the degree of anterior pituitary activation due to stress stimuli (50). However, it was also shown that changes in serotonin turnover are not necessarily reflected in the level of whole brain serotonin (49). Therefore, there is the possibility that alterations in turnover rate may be important in the activation of the pituitary by various stressors. Anesthetized dogs subjected to whole body vibration at either 4 Hz., 0.4 *g*, or 10 Hz., 2.3 *g*, for 2 hr. had an average increase of approximately 4 mcg. of 17-hydroxycorticosteroids/100 ml. plasma and a significant increase in blood epinephrine but not in serotonin (51). Therefore, although there appears to be an interrelationship between adrenergic activity and anterior pituitary–adrenocortical axis activity in the response of the living organism to environmental stressors, the role of serotonin to this activity is not clear.

Miscellaneous Endocrine Changes—Although most investigators have concentrated on the effects of stressful stimuli on the anterior pituitary–adrenocortical axis, other hormones released by the anterior pituitary have also been implicated in the stress reaction. Rats subjected to social stress demonstrated a decrease in thyroid secretion, with over 66% of the experimental animals dying within 6 days of exposure (52). The inhibition of the thyroid gland appeared to be secondary to a decline in the output of the thyroid-stimulating hormone, and there appears to be a relationship between the increased output of ACTH and the lower production of thyroid-stimulating hormone (53). Hypoglycemia stress has been reported to produce a marked depletion of growth hormone from the anterior pituitary of the rat (54). Exposure of rats to varying types of stimuli have produced different effects on the content of the growth hormone in the rat's pituitary. For example, exposure to a temperature of 3° for 60 min. produced a depletion of pituitary growth hormone (55). In the same series of experiments, the exposure to audiogenic stimuli, consisting of ringing a doorbell in the animal's cage intermittently for 30 min., elevated the pituitary growth hormone, as did spleenectomy and formalin injection. Other investigators (56) also showed that growth hormone secretion can be acutely influenced by stress. Stress has been reported to be a potent depletor of pituitary prolactin stores (57), and laparotomy and bleeding under ether anesthesia precipitously increased serum prolactin levels in the rat (58).

HIGH ALTITUDE STRESS: DECOMPRESSION AND HYPOXIA

The physiological and biochemical effects of decompression are complex in that they involve the effects induced by nonspecific stress plus the effects of hypoxia on certain organs, especially the myocardium and brain. Bernardini (59) stated that the study of aerospace pharmacology and of drug action at altitudes should include attempts to distinguish the response to an overall reduced pressure as well as the response to alterations of environmental constituent gases. Studies were undertaken in which dogs were exposed to nonhypoxic, short-term, high altitude; it was found that when glucose-tolerance tests were conducted, the results varied in response to these conditions (60–62). Chlorpromazine, amphetamine, meperidine, and diphenhydramine were given prior to a glucose loading and blood glucose decay was noted. All compounds accelerated the rate of glucose decay compared with the ground-level, nondrug condition. When the drug-injected altitude decay times were compared to the drug-injected ground-level time, those dogs injected with amphetamine and meperidine showed increased tolerance at altitude (59). The chlorpromazine-injected animals showed decreased glucose tolerance, and the dogs injected with diphenhydramine showed little or no change. These studies suggested that certain drugs which exert action on systemic glucose metabolism at ground level influence glucose handling to a different extent under nonhypoxic reduced pressure. In addition, reduced pressure alone increased glucose tolerance; therefore, it appears that within a reduced pressure environment, some factor or factors can be demonstrated independently of hypoxia.

A large number of studies have been conducted in an attempt to find compounds that could prevent or protect living organisms from the adverse effects of hypoxia. The advantages of such a compound are evident not only in a situation of exposure to high altitudes but also in many clinical conditions, especially diseases of the lungs and cardiovascular system in which the disease state leads to oxygen deficiency (63). The beneficial effects of ammonium chloride in hypoxia were believed to be due to the systemic acidosis produced by the compound (64, 65). Carbonicanhydrase inhibitors have been reported to produce beneficial effects in preventing symptoms of high altitude hypoxia (66, 67), and it has been found that carbonicanhydrase inhibitors attenuate the respiratory alkalosis seen during hypoxia. Powell and Buckley (63) reported that phenformin hydrochloride protected both anesthetized and conscious animals from the lethal effects of severe hypoxia by preventing cardiovascular collapse and CNS depression. They also found that phenformin produced marked respiratory stimulation and an arterial P_{CO_2} (partial pressure of carbon dioxide) and pH significantly lower than, and an arterial P_{O_2} (partial pressure of oxygen) significantly higher than, those observed in untreated decompressed animals.

Additional studies demonstrated that phenformin hydrochloride markedly improved the lever-press shock-avoidance performance of rats at altitudes between 5486 and 7315 m. (18,000 and 24,000 ft.) (68); however, the compound did not improve the ability of rats to learn an avoidance program at these elevated high altitudes. Rats treated with phenformin hydrochloride for 7 days demonstrated a fivefold increase in the myocardial glycogen content, as well as a marked increase in glycogen content in both liver and diaphragm (69). In these studies, blood lactate increased approximately threefold following phenformin treatment and approximately eightfold after a single dose of phenformin plus 4 hr. of decompression. The data suggest that prolonged treatment with phenformin enhances the efficiency of recycling carbohydrate under anaerobic conditions and increases utilization of carbohydrate at the expense of lipid stores. Other investigators demonstrated that hearts with greater initial glycogen stores had higher glycogenolytic rates, and proportionately more lactate was produced from glycogen than from glucose (70). Therefore, anaerobic adenosine triphosphate (ATP) production per mole of hexose was greater in hearts with higher glycogen stores. These results demonstrate that both marked and minor elevations in cardiac glycogen are associated with greater glycolytic reserve and improve mechanical resistance to anoxia. This appears to be mainly due to enhanced glycogenolysis and anaerobic adenosine triphosphate production (69). During glycolysis, 3 moles of adenosine triphosphate are generated for each mole of glycogen used, but only 2 moles are generated for each mole of glucose used. Therefore, hearts with a greater fraction of lactate produced from glycogen would have proportionately higher rates of adenosine triphosphate generation (70). These data may partially explain the protective effects produced by phenformin (65, 68) and the fivefold increase in myocardial glycogen content induced by phenformin in rats (69).

McGrath *et al.* (71) reported that there is an adaptive response to a high altitude exposure at the level of tissue function and that it could be seen as a greater capacity for the myocardium to continue to contract under conditions of oxygen lack. This response appeared at least in part to be dependent on anaerobic glycolysis and the response could be correlated with other adaptive response such as hematocrit ratio. Norepinephrine-stimulated glycolysis was markedly inhibited by severe hypoxia, and these observations suggest that reduced mobilization contributes to the loss of free fatty acids as a fuel source in the severely hypoxic puppy (72). Furthermore, these data suggest that anaerobic glycolysis needs to be considered as a factor in impaired lipolysis during severe hypoxia. Heistad *et al.* (73) subjected healthy males to a simulated altitude of 4267 m. (14,000 ft.) and found that there was decreased vascular responsiveness which was still apparent after 36 hr. of hypoxia, suggesting that adaptation of vascular reflexes had not occurred. Measurement of the response of heart rate to lower body negative pressure also suggested interference with cardiac reflexes during both acute and prolonged hypoxia. In contrast to a small increase in arterial pressure upon standing during normal atmospheric pressure and normal oxygen, their data indicated that arterial pressure falls upon standing during hypoxia. This, of course, would be expected if reflexogenic mechanisms are impaired.

Rats exposed to a simulated altitude of 4572 m. (15,000 ft.) for 17–40 hr. showed no significant alteration in ^{131}I uptake compared with ambient pressure controls (74). However, altitude-exposed rats did show an inhibition in the conversion of radio-monoiodothyrosine to radio-iodo-thyrosine and radio-iodo-thyrosine to radio-thyroxine. These data demonstrate that thyroid activity in the rat is reduced by exposure to low pressures. The authors (74) suggested that the decrease in the release of the thyroid hormone would be a definite benefit to the animals subjected to hypoxia and could be regarded as an attempt on the part of the animal to adapt itself to its new environment. The effect of hypoxia on the sympatho-adrenal system of man was investigated by measuring the epinephrine, norepinephrine, and hydroxymethoxymandelic acid excretion of adults confined to a simulated altitude of 2743–3657 m. (9000–12,000 ft.) (75). The norepinephrine excretion remained essentially the same as sea-level conditions; however, epinephrine and 4-hydroxy-3-methoxymandelic acid excretion significantly increased during exposure to low oxygen conditions. Subsequent studies performed in a low pressure chamber at sea-level conditions showed a similar response as in the low pressure chamber at reduced pressure, suggesting the importance of emotional factors during confinement to the chamber (75). Bernardini (59) found that nonhypoxic factors contributed to certain physiological responses obtained in high altitude studies; he suggested that physiological involvement may be concerned not only with an increased or decreased oxygen content but with many metabolites and enzymatic reactions involving a gas formation within a reduced pressure environment. He further stated that with the adaptations an organism makes toward environmental changes, as might be reflected in cardiovascular modifications, alterations in pulmonary mechanisms, and deviations of metabolism in general, there is a need for continued drug action studies under conditions of altitude exposure (59).

Investigators have found that amphetamine and dextroamphetamine improved the intellectual and psychomotor performance of subjects exposed to simulated altitude of 5486 m. (18,000 ft.), whereas caffeine was ineffective (76). Hypoxia markedly potentiated barbital sleeping time in mice and slightly potentiated barbital sleeping time in rats (77). On the other hand, hypoxia effectively reduced convulsions produced by semicarbazide or methionine sulfoximine. In addition, lethality due to *m*-fluorotyrosine was markedly decreased during hypoxia. Similar results obtained with exposure to low oxygen at normal atmospheric pressure or to room air at reduced pressure suggest that potentiation of the hypnotic effects of barbiturates is associated with the hypoxic environment (78). The inability of mice to gain the righting reflex under hypoxia at otherwise inadequate concentrations of pentobarbital and the prolongation of barbital hypnosis suggest an increased sensitivity of brain neurones to barbiturates (78). It appears feasible that

there is an additive effect due to the hypnotic effect of hypoxia and that of the barbiturates as well as the decrease in the metabolism of pentobarbital due to hypoxia.

Acute exposure of mice to a simulated altitude of 5791 m. (19,000 ft.) lowered body temperature and increased amphetamine lethality (79). The data in these studies suggest that the hyperthermic effect of amphetamines was not associated with the increased lethality at this altitude. A markedly increased P_{O_2} shortened hexobarbital sleep times in the intact rat while decreased P_{O_2} lengthened it (80). These changes did not appear to be related to the rate of hexobarbital transformation. A decreased P_{O_2} had no effect on the rate of metabolism of hexobarbital, barbital, zoxazolamine, phenylbutazone, sulfadiazine, and isoniazid, but an increased P_{O_2} increased the rate of disappearance of isoniazid and sulfadiazine from the plasma. Mice maintained at 5486 m. (18,000 ft.) for 5 days and then injected with 125 mg./kg. of hexobarbital had decreased sleeping times, smaller concentrations of brain hexobarbital 50 min. after injection, and increased liver microsomal metabolism of the drug compared to ground-level controls (81). These studies also suggest that the responsiveness of the receptor sites was not affected by altitude; the investigators concluded that the modification of drug action was due to stress of altitude exposure (81), since hexobarbital sleeping time is decreased by hind-limb ligation stress (82) and cold stress has been shown to affect microsomal drug-metabolizing enzymes (83). Guinea pigs born and raised at altitudes over 3657 m. (12,000 ft.) were more sensitive to the hypnotic and lethal effects of pentobarbital than guinea pigs raised at sea level (84), whereas no differences were found in the toxicity of potassium cyanide, strychnine, pentylenetetrazol (Metrazole), epinephrine, histamine, or ethanol. Administration of aspirin to rats maintained at a simulated altitude of 4634 m. (17,500 ft.) produced blood levels and a time course of these levels similar to those obtained in animals maintained at normal atmospheric pressure (85).

Local ischemia appears to be the major cause of myocardial infarction in humans and one of the most important deficiencies to the myocardial tissue is oxygen (86, 87). Environmental hypoxia induced by subjecting rats to an atmosphere of 6% oxygen and 94% nitrogen for periods ranging from 2 to 24 hr. caused myocardial degeneration in rats (88). The changes appeared within 2 hr. and were most severe at 14–18 hr., decreasing thereafter even under the continuing hypoxia. Focal necrosis became apparent in areas of degeneration at 12 hr. and was later replaced by scar tissue. A single injection of isoproterenol, 40 mg./kg. s.c., produced similar effects. Therefore, these studies suggest that the isoproterenol-induced necrosis and necrosis induced by hypoxia may be due to similar mechanisms; the authors concluded that the changes were related to the unmasking of intracellular phospholipid and to disturbance of hydrogen-transport systems (88).

In a study in which dogs were artificially respired with room air or with a mixture of 12% oxygen and 88% nitrogen, isoproterenol produced a reduction in heart rate and cardiac contractility in dogs with hypoxemia (89). Isoproterenol, in doses from 0.02 to 500 mcg./kg. administered intravenously to dogs breathing room air, produced increased heart rate and reduced arterial pressure. Propranolol, 10 mg./kg. by intravenous infusion, prevented the lethal effects of isoproterenol when administered in massive doses to dogs breathing room air; it also prevented the lethal effects of isoproterenol when administered in previously lethal doses to dogs artificially respirated with 12% oxygen and 88% nitrogen (89). These authors related their data to the increase in mortality from asthma and suggested that it may be related to the excessive use of aerosols containing isoproterenol.

Higgins *et al.* (90) studied the effects of two antihistamines upon performance of humans at ground level [381 m. (1274 ft.)], 3048 m. (10,000 ft.), and 4267 m. (14,000 ft.). Two preparations were used. Compound A contained phenylephrine, 5 mg.; phenindamine, 10 mg.; aspirin, 320 mg.; and caffeine, 16 mg. Compound B contained chlorpheniramine maleate, 2 mg.; aspirin, 390 mg.; and caffeine, 30 mg. The compound containing phenindamine did not impair performance, whereas the compound containing chlorpheniramine produced detrimental effects on performance at increased altitudes. Although these investigators found no detriment of performance with the compound containing phenindamine, it did produce some uneasiness, jumpiness, and jitteriness. The conclusions reached by these investigators using combinations of drugs and relating them to the particular antihistamine that they were interested in may not be valid, since Compound A contained phenylephrine, a potent α-adrenergic stimulant. In addition, the side effects observed with Compound A are suggestive of increased adrenergic activity.

Wistar rats, exposed to a hypoxic mixture of 8% oxygen in nitrogen for 10 min., showed a significant increase in brain γ-aminobutyric acid; exposures of increasing severity (4% oxygen in nitrogen for 10 or 15 min.) caused correspondingly greater elevations in the level of the amino acid (91). Wood (91) concluded that when animals are exposed to hypoxic conditions, a decrease in brain-oxidative metabolism, including the γ-aminobutyric acid shunt pathway, results. This causes an accumulation of γ-aminobutyric acid which depresses nerve transmission, thereby conserving the available high energy compounds by lessening the requirement of the tissue for high energy metabolites. Therefore, γ-aminobutyric acid acts as a homeostatic agent linking cerebral oxidative metabolism with the tissue function utilizing the products of this metabolism (91).

Amino acid catabolism increased in rats acutely exposed to a simulated altitude of 5486 m. (18,000 ft.) (92). This increase appears to be partially due to a caloric deficiency at high altitude and supports the concept that nutritional parameters must be considered when studying the influence of environmental extremes on metabolic response (92).

STRESS AND DISEASE

Rats subjected to chronic intermittent neurogenic stimulation developed sustained hypertension (9, 10,

93, 94). Selye (95) reviewed the principal cardiovascular lesions produced by exposure to stress or by the stress hormones that regulate the body's response during the general adaptation syndrome. Rosecrans *et al.* (96) reported that rats subjected to a condition avoidance situation developed a sustained hypertension. Other investigators failed to show that stress is an etiological factor in the development of hypertension (97). However, in these experiments in which the rat was subjected to intermittent electroshock, preceded by either a sound or light signal, the mean blood pressure of both the control and stress animals was within the hypertensive range. Plumlee (98) found that marked pressor effects could be conditioned on an avoidance design in monkeys. The avoidance schedules, however, did not produce chronic elevations in blood pressure and only transient effects were evident from the experimental design used. Squirrel monkeys subjected to intermittent stress were found to have higher mean serum cholesterol levels following the periods of stress and increased excretion of urinary 17-ketosteroids (99). Nine of 12 monkeys in the stress group were found to have atherosclerosis of the coronary arteries, whereas none of the monkeys in the control group had coronary artery atherosclerosis. Studies have demonstrated that psychological stressors may cause cardiac arrhythmias, and acute psychological as well as physical disturbances have been observed in patients in a cardiac infarction ward (100). Individuals living in an unfavorable environment develop hypertension more often than others (101); these include telephone operators under strain of heavy responsibility, Negroes and Chinese living in an unfavorable environment, animals exposed to noise and cramped accommodations, and, under certain conditions, secretaries responsible for review articles.

Systemic circulatory response to stress of simulated flight and to physical exercise prior to and following propranolol blockade was investigated by Eliasch *et al.* (102). They found that heart rate, systemic arterial blood pressure, and cardiac output increased in pilots subjected to a Link trainer simulated flight. When 5 mg. of propranolol was administered intravenously, the increase in heart rate and cardiac output was significantly less when compared to the initial flight period. The augmented response in arterial blood pressure was not influenced by propranolol; thus it appears that peripheral vascular resistance remained increased. When approximately half of the subjects were subjected to physical exercise using a bicycle ergometer with and without propranolol treatment, increases in cardiac output and arterial blood pressure associated with conspicuous falls in peripheral vascular resistance occurred; however, propranolol induced a decrease in heart rate. These authors (102) concluded that their results indicate that β-adrenergic receptor activity is extensively involved in the circulatory reaction to emotional stress. In contrast, this activity appears to be involved but less essential in the achievement of the circulatory adjustments during moderate physical exercise.

Subjects exposed to frequent and dramatic environmental changes run a higher risk of developing myocardial infarction within a relatively short period of time (67). Further studies in male rehabilitated survivors of myocardial infarction who gave weekly reports of all major life changes occurring during the previous week showed a positive and significant intrasubject covariation between the weekly sum of the life change units and the urinary output of epinephrine (103). These data further support the hypothesis concerning the role of catecholamines in the pathogenesis of degenerative heart disease possibly elicited by psychosocial stimuli (95).

Ulcer in man has been described as the classic example of a "Psychosomatic Disease" (104). Damage to the GI tract is one of the several pathological changes that results from exposure to stressors, especially immobilization stress (7). The GI changes are confined, almost exclusively, to the lower, glandular, acid-secreting portion of the stomach and appear to be microscopically and histologically similar, irrespective of the means by which the animal is immobilized (104). A combination of cold and immobilization stress (105, 106) and cold and continuous electric shock stress (107) produced gastric disorders. Rats placed in a cold room at 5–8° and subjected to continuous electric shock eventually adopted a stiff motionless posture resembling immobilization. Gastric lesions in the granular portion of the stomach were present following 8 hr. of exposure to the stressors, and 82% of the animals had these lesions following 12 hr. of stress (104). Ader (104) concluded that psychological factors do not in themselves induce ulceration; but when there is an interaction with certain physical stimuli (*e.g.*, cold, drugs, and electric shock) or a biological disposition, psychological factors can exert significant effects. The lesions of the rat's stomach, which are macroscopically and histologically indistinguishable regardless of the specific stimulus condition used to induce the lesions, suggest that despite the nonspecific nature of some of the stimuli used, there may be some common pathway or mediating mechanism responsible for the development of such lesions, which is in agreement with the work of Selye (1, 5–7).

Okabe *et al.* (108) investigated the sensitivity of experimentally induced chronic gastric ulcers in rats to cortisone treatment and exposure to stressors with emphasis on effects of the healing process. Large doses of cortisone administered from Day 1 aggravated the acetic acid ulcer by inducing a high rate of perforation. In contrast, cortisone acetate administered daily 50 days after initiation of the study had little aggravating effects. When the animals in which acetic acid ulcers had been developed (109) were subjected to acute severe stress, no further ulceration occurred (108). The authors (108), therefore, questioned the participation of stressful factors in chronicity of gastric ulcers. However, since exposure to stressors does increase plasma glucocorticoid production (1, 5), the effects of cortisone administration suggest that stress *per se* may potentiate factors contributing to gastric ulceration in the early stages.

Histological examination of gastric mucosa of mice following stress caused by restraint revealed scattered focal areas containing moderate vacuolization of cytoplasm in epithelial cells (110). Eighty-five percent of the animals under stress had reduced mitosis when com-

pared to the controls, and 90% of the animals had reductions in labeled cells. These decreases were in areas of mucosa containing no histological changes and were pronounced in areas showing the histological alterations. Therefore, despite cell damage and loss during the development of the erosions, the rate of replacement of epithelial cells was found to be significantly lower than that of the nonstress controls.

Life situations of failure, social isolation, and role crisis in male college students have been associated with those individuals seeking treatment for respiratory symptoms (111). College students seeking treatment for upper respiratory infections, asthma, hay fever, and neurosis were compared to a control group to compare the incidents of unresolved life change of students with intensities of symptomatology presented for medical care at a student health service (112). It was found that the more incapacitating the disorder, the more likely situations of life stress were reported as having occurred during the year preceding the seeking of treatment.

Investigators subjected mature female rats to auditory stimulation by an electric alarm bell at an intensity of 95–100 db. and found that exposure to this stressor prolonged estrus and increased the weight of the uterus and ovaries and that the ovaries contained mature follicles and increased number of corpora lutea (113). Auditory stimuli also apparently enhanced anterior pituitary gonadotrophic function in mature rabbits, as demonstrated by an increase in the size of the ovaries and formation of follicle hematomata and corpora lutea. Auditory stimuli induced the same changes in the genital system as those induced by stimulation of the hypothalamus or administration of gonadotrophins (113). Exposure of rats to the stress of electric shock, which was effective in activating the pituitary adrenal axis as shown by increased plasma corticosterone levels, did not induce measureable changes in adenohypophyseal LH and follicle-stimulating hormone (FSH) during a 24-hr. period following stress, suggesting that acute noxious stimuli did not have an effect on pituitary gonadotrophins (114). Exposure of rats to sound stimuli had an inhibitory effect on reproductive functions of normal rats but not on rats rendered deaf by kanamycin (113). The fertility and birth ratios of rats decreased when intensive sound, light, and electric stress were applied preconceptionally and even more markedly when neurostress was applied subsequent to mating (115). This same study demonstrated that intensive sound, light, and electric stimulation did not influence the fertilizing ability of male rats. However, when these same stimuli were applied to female rats before allowing them to begin sexual life, they affected the reproductional processes and the life conditions of the fetuses even after a prolonged period of rest (115).

Exposure of female rats to intensive sound, light, and electrical stimulation prior to conception and during pregnancy resulted in various developmental disorders in over 11% of the newborn as opposed to less than 1% in the controls (115). The most frequent disorder was cleft palate, syndactylia, and rudimentary development of the tail and hind extremities. Arvay (115) concluded that the teratogenetic effects induced by exposure of the mother to noxious stimuli were due to elevated levels of endogenous ACTH, cortisone, and epinephrine. Extreme maternal anguish has been reported to increase greatly motor activity of the fetus (116), and emotion-inducing music causes an increase in the fetal heart rate. Emotional differences created in laboratory animals by frequent handling and petting produce offspring which, at maturity, function better and are less anxious than those of mothers isolated during pregnancy (116). Humans in severe emotional states were reported to produce hyperkinetic and poorly functioning infants (116).

Sound-induced convulsive seizures were produced in several species of rodents (117–119). Henry and Bowman (120) showed that by exposing juvenile mice to 30 sec. of intensive sound, they could induce a high degree of susceptibility to sound-produced convulsions. This acoustic priming of audiogenic seizures was not effective if the mouse was not exposed to the sound source before 14 days of age and was maximal between 16 and 19 days of age. Their data suggested that priming affects some developing neurostructure during this sensitive period and varies as a function of the genetic background of the mouse. Other investigators found that the priming stimulation of susceptible mice can be either enhancement or inhibition (121). They reported that the age of sensitivity in SJL/J males begins at approximately 18 days of age and declines after 35 days of age. Mice subjected to sound stimuli at 20 days of age exhibited 90% seizure activity upon presentation of the test sound 3 days later, whereas mice conditioned at 12 or 45 days showed little response upon reexposure (122). Rats subjected to sonic stimulation not only developed audiogenic convulsive seizures but also myoclonic hyperkinesis, shock hemorrhagic states, and cerebral hemorrhage (123). Renal hypertensive rats subjected to sonic stimulation had five times the number of deaths, and hyperthyroid rats had approximately seven times the normal death rate.

ENVIRONMENTAL PHARMACOLOGY

Can environmental stimuli alter drug metabolism, drug absorption, and distribution and excretion of drugs or alter drug action through some other mechanism? These actions have been suggested in certain sections of this review, especially in relationship to high altitude stress (59, 77–79).

Investigators showed that rats subjected to the stress of unilateral hind-limb ligation showed decreased sleeping times following barbiturate administration, suggesting an increase in liver microsomal enzyme activity (82, 124). Cold stress was reported to have a stimulatory effect on hepatic microsomal drug metabolism in the rat (125). The enzymes involved in *N*-dealkylation of ethylmorphine and the hydroxylation of aniline were shown to be stimulated after 1, 2, 4, and 7 days of exposure to cold. Mean liver weights showed no tendency to increase during these periods, and the authors concluded that the increase in rate of drug metabolism was not due to increased enzyme synthesis; however, they also suggested that increased protein synthesis may be

involved in the stress-induced enzyme induction. Ryan *et al.* (126) concluded that the elevation in hepatic nicotinamide adenine dinucleotide by chlorpromazine and stress of hind-limb ligation may be due to effects on the pituitary–adrenal axis.

The stress of simulated high altitude has been found to enhance hexobarbital sleeping time (127). However, it has been suggested that the potentiation of drug-induced hypnosis during hypoxia may be related in part to the greater degree of hypothermia exhibited by mice exposed to hypobaric conditions (77). The same investigators also found a marked potentiation of barbital sleeping time during hypoxia, and they found that the pentobarbital concentration in the body declined at a slower rate in the mice exposed to hypobaric hypoxia. Their data suggest that hypoxia depressed drug metabolism *in vivo;* however, there is the possibility of decreased excretion of pentobarbital during hypoxia. On the other hand, *in vitro* studies showed that the hepatic microsomal fractions isolated from socially deprived mice metabolized hexobarbital at a higher rate than the hepatic fractions isolated from control mice and that chronic social deprivation also increased liver weight (77). Although the aggressive behavior in the male mice increased progressively from Weeks 1 to 5 of social isolation, the reduction in hexobarbital sleeping time seen after Week 1 remained at the same level throughout the succeeding weeks of isolation. Female isolated mice did not develop fighting behavior but also exhibited a decrease in hexobarbital sleeping time. The same group of investigators obtained data supporting the initial findings of Robinson *et al.* (127) concerning the effects of hypoxia on hexobarbital sleeping time and also found that social isolation enhanced microsomal enzyme activity. These results suggest that the effects of hypoxia are specific as compared to other types of stressors. The hypoxia and accompanying hypothermia may possibly be related to a general reduction in cellular metabolism and a possible additive central effect between hypoxia and the barbiturates.

The interaction of drugs affecting both central and peripheral autonomic activity and environmental stressors have been investigated in many laboratories. The LD_{50} of amphetamine is much lower in animals exposed to various types of stressors than in nonstressed animals (128, 129). Restraint stress does not enhance the norepinephrine-depleting action of amphetamines (97); stress induced by electric shock, revolving drum, and exposure of rats to 4° did not alter the brain levels of norepinephrine and serotonin or the activity of brain MAO induced by amphetamine (129). However, investigators showed that electric shock stress produced a slight increase in the levels of serotonin in the brain stem (131). Restraint stress markedly elevated 5-hydroxyindole, acetic acid, and serotonin in the mouse brain (132); these data suggest that the elevation of serotonin by stress may be associated with an increase—not a decrease—in the metabolism in the serotonin.

Adreno-demedulated rats chronically treated with guanethidine and maintained at 20° had a significant decrease in urinary output of norepinephrine (133). When the same group was exposed to 3°, there was no significant increase in norepinephrine excretion, but all of the animals died after 7 days. Control animals subjected to 3° temperature showed a threefold increase in urinary norepinephrine within the first 24 hr., and no deaths occurred in this group. These data indicate that the prevention of the increased release of norepinephrine by guanethidine was responsible for the lethal effects of cold stress since earlier studies showed that cold resistance is dependent upon increased liberation of norepinephrine (18, 134). Maickel (135) critically reviewed the interaction of drugs with autonomic nervous function and thermoregulation. Mammalian organisms maintain a fairly constant internal body temperature despite wide fluctuations in the temperature of the external environment (136). Maickel suggested that such a closely balanced thermoregulatory system depends upon sensitive and highly responsive mechanisms that must intimately involve some aspects of autonomic nervous function (136). He, therefore, investigated the effects of certain autonomic drugs on the rectal temperature of rats exposed to low environmental temperatures. Drugs were administered by intraperitoneal injection 20–30 min. prior to placing the animals in the cold room maintained at 4°. Sympatholytic agents prevented maintenance of normal body temperature by cold-exposed rats (135). Amine releasers also interfered with thermohomeostasis. Small doses of syrosingopine, which did not affect brain norepinephrine and serotonin stores and did not elicit ACTH release, also induced a significant fall in body temperature of the cold-exposed rats, suggesting the importance of peripheral sympathetic function. Guanethidine, a compound that markedly lowers peripheral stores of norepinephrine (137), also produced an inability of the mice to maintain a normal body temperature under these adverse environmental conditions. Maickel *et al.* (138) had previously shown that the effects of peripheral chemical sympathectomy could be reversed by administering epinephrine. Ganglionic blockade with chlorisondamine or pempidine produced marked decreases in body temperature of the cold-exposed mice. Central α-adrenergic blockade with phenothiazines also produced a marked fall in body temperature, with trifluoperazine being the most potent of the compounds investigated (135). The anticholinergic compounds atropine and methylatropine produced only a small but significant effect on thermoregulation; whereas the cholinergic compounds tremorine and oxotremorine were shown to cause body temperatures of cold-exposed rats to fall, despite markedly increased plasma levels of glucose and free fatty acids (136). Using the autonomic drugs as tools, Maickel concluded that the sympathetic nervous system is the messenger-control unit for the mobilization of calorigenic substrates from storage sites and that the parasympathetic nervous system is the messenger-control system for the utilization of calorigenic substrates in the production of cellular heat (135).

Increased sympathetic nerve activity has been proposed as a necessary and mediating factor in the observed stimulation of catecholamine synthesis during exposure to cold (139), and inhibition of tyrosine hydroxylase during cold exposure results in a depletion of norepinephrine in the rat heart. Ganglionic blockade

with chlorisondamine or pentolinium could eliminate phentolamine or cold-exposure-induced stimulation of catecholamine synthesis in the rat and indicates that α-adrenergic blockade and cold exposure mediate the stimulation of catecholamine synthesis *via* an increase in adrenergic nerve activity (140).

The effects of heat, cold, and work on the central action of scopolamine were investigated in healthy male volunteers at temperatures ranging from 4 to 41° (40 to 105° F.). The mental and motor impairments induced by a low dose of scopolamine were significantly increased in ambient temperatures of 35 and 41° (95 and 105° F.), and the central effects of the heat–drug stress showed no relationship to body temperature (141).

Rats maintained at temperatures ranging from 2 to 38° were treated with scorpion or rattlesnake venom, and both venoms were found to be more toxic to rats at either high or low temperature (142). Also, the greater the temperature change the greater the change in toxicity, and the toxicity of the two venoms was increased by administration of epinephrine. Since epinephrine is released under conditions of stress, the author concluded that the mechanism causing the increase in toxicity of the venoms during stress seems to be at least in part a result of the synergism between the venoms and epinephrine (142). The effects of antipyretic drugs on the change of body temperature of male albino rabbits exposed to extremes in environmental temperature showed that oral administration of these drugs exaggerated the decrease in body temperature when the animals were exposed to −5° (143). The increase in body temperature caused by raising environmental temperature from 25 to 35° was exaggerated by smaller doses of the antipyretic drugs (aspirin, acetophenetidin, antipyrine, aminopyrine, and phenylbutazone). The authors concluded that these data did not support the view that antipyretic drugs act to reset the "thermostat" of the body for normal temperature so far as the thermoregulation against heat and cold is concerned.

The stress of foot shock accelerates the metabolism of dopamine and serotonin to the same degree as norepinephrine, the only difference being that dopamine and serotonin are rapidly resynthesized, whereas norepinephrine in the brain cannot be regenerated at the same rate (144). In addition, the increased catabolism of brain norepinephrine with stress was blocked by MAO inhibitors, whereas catechol-*o*-methyltransferase inhibition with pyrogallic acid (pyrogallol) did not impede accelerated degradation.

Hypophysectomized or adrenalectomized rats exposed to cold at 4° did not demonstrate an increase in levels of plasma free fatty acids and liver triglycerides (145). However, pretreatment with cortisone restored the response to cold exposure whereas administration of epinephrine and norepinephrine did not elevate the plasma free fatty acid levels in adrenalectomized rats. The data indicate that the pituitary–adrenocortical system is important in controlling the mobilization of free fatty acids and the deposition of liver triglycerides and that the corticoids are needed to maintain the responsiveness of adipose tissue lipase to catecholamines (145). The toxicity of reserpine in adrenalectomized rats is approximately 100 times higher than that in intact animals and in hypophysectomized rats (146). The increased toxicity of reserpine in adrenalectomized rats did not appear to be attributable to failure of the pituitary–adrenal system to respond to nonspecific stress, since removal of the pituitary does not increase toxicity. Therefore, it appeared that the increased toxicity of reserpine was due to a lack of adrenal steroids.

Following administration of disulfiram, the endogenous brain levels of norepinephrine were found to be lower and the endogenous brain dopamine levels were found to be higher than in the corresponding controls (147). The increase in dopamine levels in the brain was even slightly more pronounced when the animals were exposed to cold. These investigators suggested that the increase in norepinephrine biosynthesis during cold exposure could be due to the increased formation of dopamine. Since the rate-limiting step in the formation of dopamine is the conversion of tyrosine to dopa by tyrosine hydroxylase (148), it appears that the conversion of tyrosine to dopa is increased during the exposure of animals to cold. The increase in tyrosine to dopa conversion could be due to an increase in the formation rate of dopa or to an induction of enzyme synthesis during cold exposure.

Bousquet *et al.* (149) investigated the role of endogenous histamine in the events leading to the activation of the pituitary–adrenal axis in rats following various stressors. They found that histamine release may be of significance in mediating the ascorbic acid depletion produced by stressors such as cold exposure, chlorpromazine, and formaldehyde. There was also a lack of a quantitative inverse relationship between changes in plasma corticosterone and adrenal ascorbic acid levels after exposure of the rat to various stressors.

Chronic exposure of man to emotional stressors increases plasma concentration of low density lipoproteins (150), and emotional arousal increases the plasma level of free fatty acids in man (151, 152). Nicotinic acid (niacin) was found to lower rapidly the level of free fatty acids in plasma and to inhibit effectively the stimulation of mobilization of free fatty acids from adipose tissue by norepinephrine (153). The plasma levels of free fatty acids of fasted rats treated with nicotinic acid (250 mg./kg. s.c.) were significantly reduced from 15 min. up to 3 hr., triglycerides were significantly reduced from 1 to 6 hr., and cholesterol was significantly reduced at 2 and 6 hr. (154). Liver triglycerides were significantly reduced from 2 to 6 hr. and elevated at 9 hr., whereas liver cholesterol was unaffected. Free nicotinic acid rapidly appeared in adipose tissue, and the presence of increased levels of free nicotinic acid in this tissue correlated well with the presence of reduced free fatty acid levels in plasma. The time sequence of events supports the hypothesis that the inhibition of free fatty acid mobilization caused by nicotinic acid is at least partly the cause of the depression of plasma triglyceride and cholesterol levels (154). The administration of 3 g. of nicotinic acid orally to male volunteers produced a pronounced fall in plasma free fatty acids.

During the stress period, there was a very small but significant rise in the mean free fatty acid level which was significantly lower than the rise in the untreated group. The concentration of triglycerides increased significantly in the control group and decreased significantly in the group receiving nicotinic acid (155). The authors concluded that nicotinic acid inhibited the stress-induced hyperlipoproteinemia probably by inhibiting the catecholamine-stimulated free fatty acid mobilization. The same investigators also found that although the stress-induced rise in free fatty acids was significantly inhibited by nicotinic acid and the triglyceride level actually decreased, the stress-induced increase in catecholamine secretion was not significantly affected by the nicotinic acid (156). Since elevated levels of triglycerides are frequently found in plasma from patients with coronary disease (157), this effect of nicotinic acid on plasma free fatty acids levels may have some significance in the consideration of the therapeutic approach to treatment of this disease (158).

CONCLUSIONS

Selye (1) first described the pathological, autonomic, and endocrine changes that occurred in experimental animals subjected to stressors. He concluded that these effects could be induced by various types of stressors and, therefore, were nonspecific in nature. Although this concept has been at times challenged in principle, the evidence obtained in hundreds of laboratories has reinforced the original concept. The role of the adrenergic division of the autonomic nervous system and of the anterior pituitary–adrenocortical axis in the initial phases of the stress reaction appears to be clearly defined. However, the role of other substances elaborated by various organs, especially the kidney, needs to be further elucidated. Mason (8) recently questioned the concept of nonspecificity in the stress theory. In discussing the response of the experimental animal to heat and cold, he stated: "If the organism perceives the physical stress situation as threatening enough then perhaps psychoendocrine responses do occur rather universally and are superimposed upon the endocrine and other bodily responses to the pure physical stimulus. If this interpretation is correct then the stress concept should not be regarded primarily as a physiological concept but rather as a behavioral concept." In addition, he concluded that the adrenal-cortical responses occur in many different laboratory situations involving a wide variety of stimuli, because emotional reactions occur commonly in a wide variety of laboratory situations in which animals or humans are subjected to physical stress.

Studies conducted over the past 5–10 years on both animals and man suggest that the psychological responses in man triggering the physiological and endocrine changes are induced in a manner similar to the response to physical stress by laboratory animals and man. Under certain types of environmental stimuli (*e.g.*, cold and hypoxia), factors directly concerned with the stimulus would be superimposed on the nonspecific responses obtained in the organism. However, this in no way appears to challenge the basic concept of the stress syndrome.

Evidence has also been presented by many investigators which suggests a relationship in the development of certain types of cardiovascular diseases (*e.g.*, hypertension and myocardial necrosis), gastric and duodenal ulcers, upper respiratory disorders, and CNS disorders to environmental stimuli. These diseases, which are in most cases chronic conditions, could be broadly classified as environmental diseases. Certain types of severe environmental stimuli may produce teratogenic effects which could be related to overactivity of the pituitary–adrenocortical system.

Although relatively little work has been done on the interaction of drugs and environmental stimuli, the available data strongly suggest that stress can modify drug action and drugs may modify the reaction of the organism to the stressors. Nonspecific stress, which appears to stimulate liver microsomal enzyme activity, also decreases the LD_{50} of certain drugs. Stress has been shown to increase plasma levels of free fatty acids and triglycerides which may possibly be involved in the development of certain types of cardiovascular diseases. Nicotinic acid and/or other compounds which inhibit the increase in plasma free fatty acids and triglycerides may be beneficial in the treatment of these diseases. α-Methyltyrosine, a tyrosine hydroxylase inhibitor, appears to prevent certain responses of the organism to stressful stimuli by decreasing the amount of norepinephrine in the neuronal endings. This interference with adrenergic neuronal activity could possibly prevent or attenuate the stress syndrome, thereby alleviating certain deleterious effects of exposure of the organism to noxious environmental stimuli.

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ACKNOWLEDGMENTS AND ADDRESSES

Received from the *School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15213*