1971

Cortisol and epinephrine relationships associated with stress adaptation in swine

Gerald Mark Weiss
Iowa State University

Cortisol and epinephrine relationships associated with stress adaptation in swine

by

Gerald Mark Weiss

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Meat Science

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1971

TABLE OF CONTENTS

INTRODUCTION

The interest in stress and shock associated with modern livestock production and the ultimate influence upon meat animal carcass value and muscle characteristics has resulted in an expanding knowledge of the conditions designated as (PSS) porcine stress syndrome and PSE (pale, soft exudative) pork. As our body of knowledge grows, it becomes obvious that an interrelationship of physiological and biological parameters influence stress and/or shock adaptation in swine.

The experimental objectives of this study may be summarized as follows:

1. To study the effect of alpha and beta adrenergic blockade upon adrenal activity in relation to stress.
2. To study the influence of stress upon energy and mineral metabolism.
3. To determine the composite effect of the above two influences upon carcass qualitative characteristics.

LITERATURE REVIEW

Stress and Shock

The complexity of the "syndrome" reported in this dissertation merits introductory comments within the literature review. The interrelated physiological and biochemical mechanisms involved make a segmental presentation of the literature or data a difficult task, as well as an oversimplified expression of the conditions embodied in the study of stress and/or shock.

Selye (1949) defined stress as any harmful condition resulting from the inability of an organism to maintain an adequate internal environment. Dietzman et al. (1967) defined shock as the inability of the circulatory system to meet the needs for oxygen and nutrients. The designation of PSS or porcine stress syndrome was given to a "syndrome" existing in swine displaying characteristics and manifestations of stress observed in humans as well as rats and mice undergoing various ramifications of shock (Topel et al., 1968). Sicuteri et al. (1970) stated that shock is often confused with causes that may or may not necessarily provoke it. Shock is a syndrome conditioned by a hypoxic damage of the capillaries. The causes of this condition are multiple as the term "syndrome" indicates.

According to Sicuteri et al. (1970), all medical researchers agree that shock is a single pathologic state determined by different causes. A single pathologic condition usually has a single pathogenesis i.e., hypoxia of intensity and duration that will not directly kill the animal but will cause organic damage to the capillaries. These authors suggest the etiology of shock as follows: 1) hematogenic shock (hemorrhage),

2) dynamic shock (cardiac insufficiency), and 3) autogenic shock (burns, necrosis, trauma, and antigen-antibody reactions). Shock is reversible but if prolonged becomes irreversible.

Block et al. (1966) defined shock as a catastrophic derangement of the entire circulatory system. In early medicine, shock had been attributed to a combination of cardiac failure and peripheral vascular collapse, and its treatment consisted of the application of cardiac stimulants. Crile (1899) and Cannon (1923 and 1934) directed thinking to possible toxic origin of shock in which some noxious substance induced vasodilation and capillary damage which progressed to an extent where pooling and trapping of blood no longer permitted adequate perfusion.

Blalock (1942) applied techniques for the direct measurement of blood volume and demonstrated that most forms of shock were associated with an appreciable loss in blood volume. He assumed that reduction in cardiac output was secondary to a reduction in venous return and was the initiating factor in shock. Later studies implicated other "primary" factors such as distribution of blood (Folkow, 1962; Longerbeam et al., 1962; Gourzis and Nickerson, 1965); individual organ blood flow and function (Selkurt, 1946; Selkurt et al., 1947; Baez et al., 1951; Lillehei, 1957; Rayner et al., 1960; Frank et al., 1962); destruction changes in the microcirculation (Zweifach, 1958; Hinshaw et al., 1962; Lillehei et al., 1962); and change in blood volume and vascular capacitance (Nelson et al., 1947; Lewis and Mellander, 1962). The effect of bacterial toxins as a "primary" factor of shock was given attention by Fine (1954), Weil et al. (1956), and Visscher (1958), metabolic acidosis (Huckabee, 1958a; Manger et al., 1962), proteolytic lysozymes, and the results of visceral ischemia were also studied

(Selkurt, 1959; Lillehei, 1960). Attention was also given to the role of cardiac failure in sustaining shock (Wiggers and Werle, 1942; Sarnoff et al., 1954; Guyton and Crowell, 1961; Bing and Ramos, 1962).

Block et al. (1966) summarizes shock as a progressive circulatory failure in which the cardiac output is insufficient to meet tissue requirements for nutrition, oxygenation, or waste disposal: the major initialing and sustaining mechanisms are decreased cardiac output, increased systemic peripheral resistance, and decreased effective circulatory blood volume, each of which feeds back either directly or through the sympathetic nervous system to perpetuate the shock cycle; this results in increased adrenergic activity stimulated by baroceptor-monitored hypotension. The response to this activity is a selective reduction of blood flow to the splanchnic viscera and to the skin. This produces the clinical signs of shock - pale, cold, moist skin, slow capillary filling, and oliguria. Hypotension is a secondary, not a primary, manifestation of shock. Prolonged reduction of blood to vital visceral areas leads to several potentially lethal changes including metabolic acidosis, parenchymal cell destruction with the release of vasoactive, proteolytic, and toxic substances from disrupted lysosomes, progressive loss of capillary integrity with extracellular fluid shifts, leakage of plasma, and stagnation and pooling of blood (Block, 1966).

Circulation

Lillehei et al. (1964) stated that hemodynamic disturbances resulting from shock due to hemorrhage or endotoxin vasopressors intensity the visceral vasoconstriction, ischemia, and loss of capillary integrity charac-

teristics of severe shock. The hemodynamics of shock appear to be similar in man and animals although the visceral organ which suffers the greatest injury varies among the species. The importance of the intestine lies in the susceptibility of its arterioles and venules to the vasoconstriction occurring during shock, the massive amount of tissue destruction alone resulting from the anoxia being enough to cause the death of the animal.

Prolonged vasoconstriction accompanying shock causes enough cellular damage alone, due to mechanical limitation of blood flow and attendant stagnant anoxia, to result in irreversible shock. This is the oldest theory for the explanation of irreversible shock (Malcolm, 1905; Bainbridge and Trevan, 1917; Erlanger and Gasser, 1919; Cannon, 1923; Freeman, 1933). More recent suggestions propose that slugged blood forms resulting in intravascular aggregation, agglutination, and thrombis and, thus, initiate the state of irreversible shock (Kinsely et al., 1945; Heimbecker and Bigelow, 1950; McKay et al., 1955; Gelin, 1956; Hardaway and Johnson, 1963).

Events leading to the irreversible state are initiated with the spasm which affects both venules and arterioles and results in an ischemic capillary bed. As the shock is prolonged, the continued ischemia results in relaxation or loss of tone of the precapillary sphincters (resistance vessels). This relation is probably a consequence of ischemia and local acidosis in the surrounding tissues (Lillehei et al., 1964). Further work reported by Lillehei et al. (1964) showed that the postcapillary sphincters (capacitance vessels) on the venous side are more resistant to anoxia and acidosis of shock and maintain their tone even while the resistance vessels are failing. As a result, blood begins to fill the capillary beds, and a shift from ischemic to stagnant anoxia occurs. Thus, an increasing share

of the blood volume is sequestered from the active circulation and causes an increase in the hydrostatic pressure within the congested bed. The inevitable result is a forcing of plasma into the tissues where it is lost from the active circulation. Additional investigation by these authors indicated that the heart is able to function completely with a good output if it is provided with adequate venous return and a reduced peripheral resistance, even after prolonged shock and in the face of necrotic bowel and other visceral damage.

Block et al. (1966) stated that hypotension occurs in shock as a consequence of reduced cardiac output and diminished circulatory blood volume and despite an increased peripheral resistance. The state of reduced perfusion before blood pressure falls has been called "compensated shock" while hypotensive shock is referred to as "decompensated shock". In general, shock is a low cardiac output, high peripheral resistance state of circulatory failure.

Wiggers (1947), Guyton and Crowell (1961), Crowell and Guyton (1962), and Braunwald (1965) all demonstrated the major component in many forms of shock to be left ventricular failure and its consequence is reduced cardiac output. During shock, the heart attempts to perform its work while its nutrient requirements exceed the supply. Prolonged restriction of microcirculatory inflow and outflow renders the capillary bed ischemic with resultant local acidosis (Lewis and Mellander, 1962).

Dietzman et al. (1967), in an extended summary of the treatment of shock, stated that flow or cardiac output is dependent on adequate venous return and on myocardial muscular contraction or the inotropic function of the heart. The central venous pressure is a measure of venous return and

the ability of the heart to handle this return. Systemic or peripheral resistance is governed by the pre and postcapillary arterioles and venules, which are under the influence of the sympathetic nervous system, and by the viscosity of the blood.

In hemorrhagic shock, a decrease in blood volume causes a reduction in venous return and central venous pressure and a consequent decrease in cardiac output and blood pressure. This decrease in pressure activates the carotid and aortic baroreceptors which in turn stimulate the sympathetic nervous system. The resultant outpouring of epinephrine and norepinephrine from the adrenergic nerve endings and the adrenal medulla produces vasoconstriction and increases peripheral resistance; thus blood pressure is increased (Dietzman et al., 1967).

In cardiogenic shock, primary "pump failure" due to a decrease in the inotropic function of the heart reduces cardiac output and stimulates the baroreceptors to activate the sympathetic nervous system. The blood volume initially remains unchanged, and the rise in central venous pressure mirrors the degree of cardiac failure. Yet in cardiac failure, stagnation in underperfused areas of viscera and skin eventually reduce the effective circulatory blood volume and causes further sympathetic response.

Thus, a decrease in cardiac output due to an absolute volume reduction, as in hemorrhagic and endotoxin shock, and that due to a reduction in the inotropic function of the heart caused by myocardial damage, as in cardiogenic shock, activate the same baroreceptor mechanisms. Consequently, the peripheral microcirculatory disturbances which result are identical for three causes of shock. If the inequitable redistribution of blood flow to the viscera and skin is prolonged or intense enough, death may occur from

the effect of ischemia in these areas. Redistribution of blood flow to all tissue beds by the reduction of vasoconstriction increases survival.

All three forms; hemorrhagic, endotoxin, and cardiogenic forms of shock, are associated with a fall in blood pressure, cardiac output, and splanchnic blood flow and a rise in peripheral resistance and circulating catecholamines. The overall picture in all three forms of shock is one of peripheral vasoconstriction and reduced tissue perfusion due to arteriolar and venular constriction. Because of the difference in action of norepinephrine and epinephrine on various organs, the effects of norepinephrine have been attributed to alpha receptors and those of epinephrine to beta receptors. The corresponding neurohumoral effects restrict blood flow in the skin, bowel, liver, kidney, and lung and permits preferential perfusion of the heart, brain, and muscle. Although this inequitable redistribution of blood flow is initially lifesaving, its perpetuation by the use of vasopressor agents does not improve survival.

Theoretically survival should be improved by the reestablishment of equitable blood flow to all tissues. Practically, this can be accomplished by the administration of vasodilating agents in combination with volume replacement. By increasing venous return to the heart with volume expanders, organ blood flow can be improved.

Cardiogenic, hemorrhagic, and endotoxin forms of shock in man are characterized by reduced organ perfusion and vasoconstriction. Clinically, these changes are expressed as a reduction in urinary output due to renal ischemia and pale, cool extremities due to reduced skin perfusion. Patients with hemorrhagic or cardiogenic shock have reduced cardiac output and increased total peripheral resistance. The central venous pressure is

lowered in hemorrhagic shock; in cardiogenic shock, it is either normal or slightly elevated. The blood pressure may be either normal or reduced, which reflects the dependence of this reading on both the cardiogenic output and the magnitude of peripheral vasoconstriction. In endotoxin shock, cardiac output is often normal or elevated in contrast to the reduced cardiac output seen in animal experiments. This discrepancy is related to the diverse effects of the gram negative bacteria.

The circulatory changes in shock, although induced by various means, comprise the symptoms of decreased cardiac output and increased peripheral resistance. These symptoms have persisted to the present time with the recent addition of intravascular coagulation as a component of hemodynamic change (Wilson et al., 1967; Hirshfeld and Fell, 1969). Blood pooling and perfusion also accompanies shock in a majority of cases (Perlroth and Harrison, 1969; Armstrong, 1970). Once the shock syndrome develops, physiologic compensatory mechanisms are activated. These include stimulation of baroreceptor reflexes and the recruitment of the extravascular fluids into the vascular compartment. The regulation of cardiovascular performance is altered, as is distribution of blood flow, in order to favor the brain and heart. With progression of the lesion and failure to restore normal circulatory dynamics, hypotension deepens, metabolic acidosis occurs, and frequently arterial hypoxemia is found (Peretz et al., 1965; Neaverson, 1966). Death due to shock has been attributed to pulmonary lesions, disseminated intravascular coagulation, and disturbance of the normal clotting response associated with a coagulation defect (Hardaway et al., 1967).

Lesh and Rothe (1969) demonstrated elevation of vascular volume in response to sympathetic nerve excitation and to flow and pressure changes.

They summarized their work stating that no conclusive evidence was found to substantiate that neurogenic vasoconstriction in skeletal muscle was responsible for translocating functionally important amounts of blood to the central circulation.

Carlo (1970) stated that the primary factor involved in the pathogenesis of the irreversible state of the peripheral circulatory insufficiency is an endotoxemia due to the loss of the detoxifying function of the reticulo-endothelial system consequent to a prolonged ischemic damage by sympathetic overactivity. The data supporting this hypothesis is derived from observing that the liver and spleen are able to extract and detoxify endotoxin. Thus, the detoxification is a function of the reticulo-endothelial cells since these are the only cells common to both organs. The function involved by the reticulo-endothelial system of both organs is presumably concerned with the extraction of a vascular toxin, which is vasoactive because it cannot act upon a denervated tissue. Various vasoactive substances such as histamine, serotonin, catecholamines, etc. can be identified in the blood of dying animals subjected to stress or shock. However, these compounds cannot be implicated in the genesis of the peripheral circulatory insufficiency because the reticulo-endothelial system is not known to be capable of clearing any of them.

Hemodynamics are also influenced by vasoactive compounds designated as kinins. Roch e Silva (1970) proposed evidence of the participation of the kinin system in the etiology of different manifestations of shock based on the following: 1) activation of proteolytic or esterolytic enzymes in many kinds or shock, 2) variations of the bradykiniogen content of plasma following the injection of proteases, animal venoms or in different kinds of

shock, 3) detection of free kinins in the blood under shock-like conditions, 4) activation of kinin-systems in in vitro conditions produced by tissue trauma or the action of shock-producing agents i.e., trypsin, animal venoms, and cellulose sulfate, and 5) by the use of inhibitors of the kininogenin-kininogen system. Berry et al. (1970) reported that when anesthetized dogs were bled to produce hypotension, kinins appeared in the circulation equivalent to 1-4ng/ml bradykinin. When the blood pressure was restored, this output was reversed.

Armstrong (1970) stated that the intrinsic potential of serum for producing vasodilator substances such as kinins is very great during the manifestations of shock. According to Armstrong and Stewart (1960), Armstrong et al. (1966), and Armstrong (1969), the very high kinin-forming potential of body fluid and tissues is in sharp contrast with the minute concentrations of kinins required for biological effects. A small fraction of the total potential is sufficient to produce any of the pathological changes attributed to kinins-vasodilation and an increase in capillary permeability.

Another component of the plasma capable of producing vasodilation increases in the capillaries and a fall of blood pressure is the anaphylatoxin system. This appears to operate mainly by means of histamine which is released from the tissues (Hahn and Oberdorf, 1950; Roch e Silva et al., 1951; Hahn et al., 1954; Roch e Silva, 1954; Dias da Silva and Lepow, 1965; Dias da Silva and Lepow, 1967).

Various chemical factors have been reported as placing a controlling influence upon circulation (Dale, 1929). Armstrong (1970) suggested that kinin-forming systems of the human serum or plasma also produce vasodilator, hypotensive substances - polypeptides. Schauer et al. (1970) demonstrated

the adaptive histamine formation in endotoxin shock, further substantiating the variability of contributing factors to shock induced changes in hemodynamic mechanisms in contemporary research. Schneider (1970) demonstrated that intravascular coagulation or fibrinolysis can cause or be caused by circulatory shock.

In cardiogenic shock, Hinshaw et al. (1961) demonstrated vasoactive amines, and Lefer et al. (1967) showed that peptides are released into the circulation; the clotting mechanism is altered (Crowell and Read, 1955; Hardaway et al., 1967).

Selkurt (1970) reported the so-called "irreversible phase" of shock involving generalized failure of circulation in the posttransfusion phase, inclusive of several parameters: fluid loss or shifts between compartments, peripheral circulatory failure, and myocardial failure. Increasing evidence is accumulating of release of vasoactive agents from specific sites e.g. intestine and pancreas, which might have a depressing effect on the heart or have a deleterious action on the peripheral circulation. Lefer (1970) stated that a myocardial depressant factor has been found in the plasma of cats and dogs in postoligemic shock. The myocardial depressant factor (MDF) appears to be a peptide or glycopeptide with a molecular weight of 800-1000. The hydrolytic enzymes (proteases), which are thought to catalyze the formation of MDF, originate from the ishemic splanchnic region, probably in large part from the pancreas. MDF depresses the myocardium in isolated cardiac tissue and in the intact animal. High plasma MDF activity is associated with short survival times in shock. Accumulation of MDF in the plasma may be prevented by pretreatment with high concen-

trations of glucocorticoids, protease inhibitors, pancreatomy, or hemodialysis.

Stress, Shock, and the Adrenal Gland

Adrenal medulla hormones

The integration of various components of shock; hemodynamics, neural-humoral factors, metabolic parameters, and environmental influences, have been either suggested or reviewed in detail in the previous section. This portion of the literature review will deal with the primary endocrinological ramifications of the adrenal gland involvement in stress and shock.

Topel (1968a) reported that little literature was available involving stress and/or shock in domestic meat animals. Krogh (1929), Zweifach (1968), and Baez and Orkin (1963) concluded that the regulation of microcirculation is partially influenced by neurohormonal events mediated through the interaction of blood born principles and agents arising locally in the tissues.

Current concepts of local regulation of blood flow postulate a balance between vasodilator and vasoconstrictor factors (Zweifach, 1961; Baez and Orkin, 1963). Dilators such as histamine (Shayer, 1963) and acetycholine (Bean and Sidky, 1958), kinins such as bradykinin (Hilton, 1962), constrictors and dilators such as catecholamines (Zweifach, 1961), posterior pituitary hormones such as vasopressin (Bartelstone and Nasmyth, 1963), and the adrenal cortex hormones such as 17-hydroxycorticosteroids (Sechzer et al., 1960) are some of the important substances associated with vascular homeostasis.

The action of catecholamines in an effector cell is thought to be exerted through one or the other of two types of receptive mechanisms or receptors referred to as α and β (Ahlquist, 1948). The α receptor is associated with most excitatory functions such as vasoconstriction, and the β adrenotropic receptors are associated with inhibitory functions such as vasodilation (Youmans, 1967).

Norepinephrine functions by intra-arterial constriction of muscle blood vessels in all effective doses (Folkow and Uvnas, 1948; Barcroft and Knozett, 1949; Cabbold and Voss, 1953; Celander, 1953; Whelan, 1954). Intravenous norepinephrine constrictor action may be overcome by the rise in blood pressure; if this is prevented (Cabbold and Voss, 1953) or obviated, the muscle vessels constrict.

Epinephrine causes vasodilation in skeletal muscle, and when a mixture of epinephrine and norepinephrine are injected directly into the arterial blood supply of the muscle, it appears that minimal effective doses act on β receptors only, and epinephrine is much more potent than nonepinephrine (Youmans, 1967). The metabolic, calorigenic, and vasodilation effects of epinephrine are greater than norepinephrine.

With larger intra-arterial doses of epinephrine or norepinephrine, the effect on the α receptors in skeletal muscle becomes more and more prominent and tends to override the effect on β receptors. Therefore, on skeletal muscle, epinephrine is a good vasodilator while norepinephrine is a poor vasodilator, and at higher doses, it may produce an overall vasoconstrictor action while similar doses of epinephrine produce vasodilation (Youmans, 1967). The net effect of most doses of norepinephrine is to produce an increase or decrease in peripheral resistance. Thus, a given dose

of norepinephrine may produce a greater rise in blood pressure than that produced by the same dose of epinephrine but probably would produce a lesser increase in blood flow in skeletal muscle (Barcroft and Knozett, 1949; Van Harreveld et al., 1952; Lanier et al., 1953; Barcroft, 1962).

It appears that muscular fatigue from stress in an adrenal insufficient animal is not due to an impaired musculature or myoneural junction but to a circulatory collapse (Ramey and Goldstein, 1957). When an animal is stressed, epinephrine release produces a shift of blood flow from the splanchnic area to the working muscle (Ramey et al., 1951). In the absence of adrenal cortical steroids, the threshold for epinephrine and norepinephrine action is greatly raised, and, therefore, when an adrenal insufficient animal is stressed, splanchnic engorgement occurs due to the abnormal shift of blood from the splanchnic region to the skeletal muscle, and a vascular collapse occurs (Ramey and Goldstein, 1957).

It appears that the adrenal insufficient animal attempts to compensate for the lack of effective effector-organ response to sympathetic stimulation by increased activity within the system (Sheehan, 1948). The high titer of constrictor materials released ultimately acts to destroy the responsiveness of the small blood vessels. Administration of steroids up to a certain point will protect the effector organs against these effects (Fritz and Levine, 1951; Ramey and Goldstein, 1957), but even the intact animal with a functional adrenal cortex finally succumbs to excessive sympathetic bombardment (Overman and Wong, 1947; Wiggers et al., 1948· Topel et al., 1968b).

Romanul (1965) reported that skeletal muscle fibers with low oxidative metabolic activity are those which derive their energy from anaerobic gly-

colysis and are, therefore, highly influenced by the action of epinephrine (white fibers) in contrast to red fibers which don't store as much energy and need blood to bring energy to them as well as oxygen. Cooper et al. (1969) showed that stress prone pigs have considerably fewer red fibers than stress-resistant pigs which indicates abnormal characteristics in both metabolic and micro-circulatory function.

According to Youmans (1967), any influences of the autonomic nervous system on skeletal muscular activity must be exerted either 1) through influences on the blood vessels in skeletal muscle, 2) through influences on the blood flow related to alterations in pressure, 3) by altering transmission of excitation at the motor endplates, or 4) by affecting contractility of muscle fibers. Cannon (1929) emphasized that mass discharge of the sympathoadrenal system occurs in certain situations which lead to large changes in the internal environment.

As early as 1904, Elliot stated that the sympathetic axons cannot excite the peripheral tissue except in the presence and perhaps through the agency of adrenaline or its immediate precursor secreted by the sympathetic paraganglia. Adrenaline might then be the chemical stimulus liberated on each occasion when the impulse arrives at the periphery. Considerable quantity of the catecholamines is stored in the terminations of the axons of adrenergic neurons and in chromaffin cells of the adrenal medulla (Youmans, 1967).

The adrenergic transmitter is released to exert an influence in cells of effector organs, as mentioned previously. The most important effector organs, according to Youmans (1967), include smooth muscle, cardiac muscle, the cardiac conducting system, and secretory cells in various glands.

Norepinephrine and epinephrine act through two types of receptors, previously referred to as α and β, and this is especially true in smooth muscle (Youmans, 1967). The basis for the two receptor mechanisms is as follows: 1) Catecholamines cause opposite effects in smooth muscle in different locations, 2) removal of a chemical group from or addition of a radical to the epinephrine molecule may alter potency greatly with regard to some effectors while altering its potency little in other effectors, and 3) specific agents may block effects on smooth muscle in certain sites and not block effects on smooth muscle in other sites (Youmans, 1967). The α receptors are sensitive to the action of epinephrine and are blocked by drugs such as phenoxybenzamine. β receptors are also sensitive to epinephrine, but this response is blocked most effectively by drugs such as dichloriso-proterenol and propanolol (Youmans, 1967).

Stimulation of the sympathetic nerve which terminates in the smooth muscle of the arterioles of skeletal muscle or the injection of epinephrine into the artery which supplies a muscle will result in an increase in amplitude of contraction of the muscle in response to supramaximal stimulation of its motor nerve if the muscle is in a state of fatigue as a result of previous prolonged stimulation or if the blood supply to the muscle is impaired or both. However, the absence of fatigue of the muscle and in the absence of impairment of the blood supply to the muscle, sympathetic nerve stimulus, splanchnic nerve stimulus, or injection of epinephrine has less effect on amplitude of the contraction of muscle in response to single supramaximal stimuli applied to the motor nerve (Youmans, 1967).

Catecholamine influences on muscular activity involves three problems: 1) the ways by which they can influence blood flow in muscle, 2) the ways

by which they can affect transmission of excitation at the motor endplate, and 3) the ways by which they can influence the contraction of the muscle.

Specific catecholamine influences have been recognized by Dietzman et al. (1967) in the case of hemorrhagic shock. A decrease in blood volume causes a reduction in venous return and central venous pressure and a consequent decrease in cardiac output and blood pressure. This decrease in pressure activates the carotid and aortic baroreceptors which in turn stimulate the sympathetic nervous system. The resultant outpouring of epinephrine and norepinephrine from the adrenergic nerve endings and the adrenal medulla produces vasoconstriction and increases peripheral resistance, thus, blood pressure is increased. Both norepinephrine and epinephrine cause cardioacceleration. The sympathoadrenal stress response is greatest in the vasoactive, adrenergically sensitive viscera and skin. The α receptors in these areas are sensitive to the outpouring of catecholamines from the adrenal medulla and sympathetic nerve endings and respond by vasoconstriction.

Dietzman et al. (1967) and Novelli et al. (1970) both reported splanchnic vasoconstriction leading to preferential circulation to the heart, brain, and lungs induced primarily by catecholamines and probably histamine and kinins as well. Berk et al. (1967) reported that intravenous infusions of epinephrine in dogs in amounts capable of producing shock and yet within endogenous secretory limits cause highly significant increases in the portal vein flow, oxygen pressure, and the femoral vein oxygen pressure. These biological changes are thought to be caused by the opening of multiple arteriovenous shunts in these areas with epinephrine causing the opening in the pulmonary area.

The opening of these arteriovenous shunts is thought to set off a hemodynamic chain of events resulting in shock. Similar hemodynamic changes occur in shock of various causes all having in common elevated epinephrine blood levels. These findings refute in part the commonly accepted vasoconstrictor theory of shock. Instead of excessive vasoconstriction due to epinephrine which causes the detrimental effects of late shock, it is suggested that the opening of multiple arteriovenous shunts sets off a hemodynamic reaction that is primarily responsible.

The literature involving adrenalectomized animals is very expansive. Fritz and Levine (1951) adrenalectomized rats and subjected them to physical stress. The adrenalectomized animals died of circulatory failure in response to stresses to which the normal rats adjusted. Blood vessels of the adrenalectomized rats became refractory to repeated applications of norepinephrine, while those of normal controls retained their sensitivity. Responsiveness to norepinephrine was restored by the topical application of cortical steroids which appear necessary to allow blood vessels to respond regularly and repeatedly to minute amounts of epinephrine and, at the same time, to prevent the toxic effects upon blood vessels of large amounts of norepinephrine.

Since the time of Erlanger and Gasser (1919), it has been repeatedly confirmed that the continuous intravenous infusions of epinephrine at relatively high rates causes an irreversible shock in dogs. Noxious effects of epinephrine upon the cardiovascular system are determined by the level of plasma epinephrine in arterial blood. This depends not only upon the rate of epinephrine infusion but also upon the rate of its removal from the circulation which is known to proceed rapidly (Jones and Blake, 1958).

Fukuda et al. (1967) induced epinephrine shock by epinephrine infusion and observed an inability to maintain the initial stationary level of plasma epinephrine leading to a progressive rise of epinephrine up to as much as 300-400 µg/l. Administration of glucocorticoids markedly potentiated the epinephrine removing capacity of the liver, while adrenalectomy reduced it.

Frankenhauser et al. (1961) compared epinephrine and norepinephrine administration with regards to mental and physiological responses. Epinephrine responses surpassed norepinephrine influence when heart rate, arterial pressure, and urinary catecholamine excretion were observed. The results were interpreted to indicate that an increased alertness accompanying the emotional changes produced by the catecholamines may act to counterbalance other unfavorable effects on performance.

Jersild and Thomas (1931) examined the effects of subcutaneous injections of adrenaline hydrochloride and found a slight improvement in motor tasks. Landis (1935) investigated the influence of subcutaneous injections of adrenaline on complex muscular activity and found no impairment in speed or accuracy. Basowitz et al. (1956) found that motor performance was slightly impaired during prolonged intravenous adrenaline infusion at a low dose level, whereas performance in other types of tasks was not affected.

Data provided by studies of performance in other types of stress situations are similarly contradictive. The problem is highly complex, and stress may both aid and interfere with performance depending upon a number of factors such as degree and nature of the stress, the type of performance, as well as the various personality traits of the subject (Lazarus et al., 1952; Steinberg, 1959).

Gellhorn (1943) stated that the adrenal medulla as part of the sympathetic nervous system is intimately connected with specific emotional expression. Another characteristic of the sympathetic nervous system is the variation in levels of integration represented by structural and functional components involving the cerebral cortices, midbrain, and hypothalmus as well as the peripheral effector components (Elmadjian et al., 1958). These authors studying normal and psychiatric patients in experimental and life situations support the hypothesis that active aggressive emotional displays are related to increased excretion of norepinephrine, whereas tense, anxious, but passive, emotional displays are related to increased excretion of epinephrine in association with normal excretion of norepinephrine.

Yamori et al. (1970) found norepinephrine concentrations in lower brainstem, and the hypothalmus of genetically hypertensive rats are significantly lower than in control rats. These authors suggested that catecholamine mechanisms in the central nervous system may play an important role in the regulation of blood pressure and genetic hypertension in the rat.

von Euler (1964) suggested quantitation of stress by catecholamine analysis. He based this possibility on the observation of gravitational stress and exposure to cold which are mainly associated with an increase in the norepinephrine excretion, indicating the importance of this hormone in circulatory and temperature controlling homeostatic mechanisms. Mental stress involving aggressive reactions is also associated with an increase in the norepinephrine excretion. The types of emotional stress which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion.

Thus, the possibility of obtaining a graded response from the adrenal medulla suggests that mental stress situations may be quantitatively evaluated by urine catecholamine analysis.

Hyperfunction of the adrenal cortex is termed Cushing's syndrome in man. Characteristics of this abnormality are hyperglycemia and muscular weakness. Muscular weakness, in addition to low blood pressure, impaired appetite, gastrointestinal upsets, and discoloration of the skin and eventual death are symptoms of Addison's disease or hypofunction of the adrenal cortex (Turner, 1960).

Adrenal cortical hormones

Circulating 17-hydroxycorticosteroids (17-OHCS) levels have been implicated in progressive muscular dystrophy (PMD) where there is a significant decrease in urinary (17-OHCS) indicating an inadequate formation and excretion of hydrocortisone. A single test injection of ACTH showed variations in the functional state of the adrenal cortex in different groups of patients with PMD suggesting that only some individuals have adequate reserves of adrenal 17-OHCS. Multiple injections of ACTH frequently revealed a secondary type of adrenocortical insufficiency. Several individuals were also found to have an insufficiency of potential reserves indicating a disturbance of adrenocortical function. Cases of PMD have revealed impairment of hormone formation by the adrenal cortex (Shagal and Shraiberg, 1964).

The secretions of the adrenal cortex play an undisputed role in the defense of the organism against all sorts of noxious agents (Swingle and Remington, 1944). Adrenalectomy renders an animal much more susceptible to

a variety of traumatic procedures, as well as to the injection of endogenous or exogenous toxins, all factors which in the end have a damaging effect upon the peripheral vascular system. The adrenalectomized animal, when submitted to these noxious agents, eventually dies from circulatory failure, which can be attributed to a collapse of the peripheral circulation (Wyman and Tum Suden, 1939; Selye, 1950; Halpern and Wood, 1950a,b).

Treatment with whole cortical extracts or with desoxycorticosteroid (Swingle and Remington, 1944) restores to the adrenalectomized animals at least part of their natural resistance to various forms of stress. Halpern et al. (1952) reported that in hemorrhagic shock induced in adrenalectomized rats by repeated and graded hemorrhage, cortisone and, to a lesser extent, desoxycorticosterone each produce a definite protective effect. Desoxycorticosterone cannot maintain either the blood pressure or the body temperature as well as cortisone does.

These researchers also reported that in histamine shock, desoxycorticosterone does not modify the high sensitivity of adrenalectomized mice to histamine, whereas cortisone increases this tolerance about five times and adrenaline ten times. None of these three hormones can alone restore the natural resistance to histamine in the adrenalectomized animal. Thus, cortisone and, to a lesser extent, desoxycorticosterone enhance the resistance of animals to traumatic and toxic injuries by improving the ability of the small vessels to respond to the exogenous and endogenous vasoactive agents.

Studies by Ramey et al. (1951) lead to the conclusion that the presence of adrenocortical hormones were essential to provide a "permissive" action for the pressor effect of catecholamines. The effectiveness of glucocorticoids have been evaluated by their inhibitory effect upon their

induction of histamine forming activity in the liver, the "shock organ" in dogs by Fukuda and Fukuda (1969). The mechanisms of the anti-shock effect of glucocorticoids in adrenalectomized animals might differ depending upon the animal species, just as the mechanism of shock itself differs.

Houck and Gladner (1970) proposed mechanisms for the ameliorative effects of corticosteroids in shock. These are as follows: 1) cortisol induces the synthesis of at least three proteolytic and one collagenolytic enzyme which appears in the extracellular compartment of rat skin, 2) the proteases digest fibrin and can activate plasminogen, 3) the proteases destroy bradykinin very rapidly, 4) the collagenases release products of collagenolysis which can be degraded to free amino acids which in turn are powerful inducers of liver glyconeogenesis and, hence, can provide reserve energy to the host, and 5) therefore, steroid induced enzymes might be important in restoring the microcirculatory blood flow (via fibrinolysis and the destruction of bradykinin) and for providing extra energy (via the collagenolysis and consequent liver glyconeogenesis) to the patient in shock.

Lefer and Verrier (1970) supported the significance of corticosteroids in the regulation of circulatory function and that in their absence there is circulatory collapse. The predominant feature of this collapse is impairment of myocardial function. Physiologic concentrations of corticosteroids are effective in preventing or reversing the circulatory collapse observed in adrenocortical insufficiency.

Circulatory shock is characterized by markedly elevated secretions of corticosteroids with reduced catabolism of steroids. In general, pharmacologic concentrations of glucocorticoid administration prior to shock

increase survival and tend to normalize circulatory function in hemorrhagic, endotoxin, snake venom, anaphylactic, and surgical shock. The mechanism of the glucocorticoid protective action in shock appears to be related to lysosomal membrane stabilization and prevention of kinin formation (Lefer and Verrier, 1970).

Thus, corticosteroids exert prominent effects on the cardiovascular system (Gross, 1960; Gross, 1961). The circulatory effects of the corticosteroids have been under investigation since 1849 when Addison recognized that cardiovascular collapse was a prominent feature of adrenal insufficiency. The cardiovascular effects of corticosteroids are of considerable interest because hypotension is a prominent feature in adrenocortical insufficiency, and hypertension occurs in hypersecretion of adrenal corticosteroids.

Altura (1966) designed experiments to evaluate further the proposed role of "intrinsic histamine" and glucocorticoids in the local regulation of blood flow. Various pure synthetic glucocorticoids, even when given in large doses, did not constrict any of the muscular components of the capillary beds. These steroids, however, enhanced vascular reactivity to various constrictors while suppressing histamine and bradykinin-induced vasodilation. Furthermore, these steroids were able to restore microvascular responsiveness to constrictor materials whose peripheral actions had been suppressed or absent in animals depleted of their mast cells. These findings reinforce the hypothesis that glucocorticoids may function as regulators of local blood flow via their modulation of vascular smooth muscle responsiveness to other endogenous humoral agents.

Motsay et al. (1970) reported a prime factor causing mortality from septic and cardiogenic shock is stagnant microcirculation which is not always corrected by administration of fluids and is often worsened by the use of vasopressors. Massive doses of corticosteroids, but not a physiological dose, would counteract the lethal effects of large doses of epinephrine on the cardiovascular system. Epinephrine and norepinephrine are vitally supplied in the body's rather nonspecific response to trauma, sepsis, or cardiac damage. Their effect is principally on the microcirculation of the viscera and skin and characterized by an initial ischemia due to arteriolar and venular constriction, followed in a greater or lesser time by stagnation in which arteriolar tone is lost but venular constriction remains. Accompanying this stagnant phase is increased capillary permeability leading to further fluid loss and aggregation which may be followed by intravascular thrombosis and coagulation defects. Massive doses of corticosteroids such as methylprednisolone given to animals or man in shock can apparently prevent these changes from occurring if given before terminal shock developed.

Lillehei et al. (1964) reported that pretreatment with hydrocortisone in large doses protects the cell against the pernicious effects of prolonged ischemia. The hemodynamic disturbances resulting from epinephrine injection in the dog closely resemble conditions of hemorrhagic and endotoxin shock. The noxious effects of epinephrine can be blocked by pretreatment with phenoxybenzamine or other adrenergic blocking agents and hydrocortisone.

Lillehei et al. (1965) state that hydrocortisone is an effective drug to use alone, in contrast to phenoxybenzamine, although results are

improved if it is combined with fluid therapy. The need for fluid therapy becomes more acute as the time between the onset of the shock and the initiation of treatment is increased. Giving hydrocortisone alone in the face of hypotension will not cause any further hypotension; the blood pressure often rises almost immediately after its administration. The effect of large doses appears to be a gradual reduction in individual organ and total peripheral resistance with restoration of cardiac output and restoration of more normal fluid to the bowel and other visceral organs. Plasma volume losses are curtailed, catecholamine levels decrease, venous return and cardiac output increase, and urine flow is restored.

Lillehei et al. (1964) reported that administration of hydrocortisone results in no depression of blood pressure or other vital signs in contrast to phenoxybenzamine. Rather there is often an elevation of pressure after hydrocortisone administration even before additional plasma or blood is given. Phenoxybenzamine is likely to cause a further blood pressure fall as the size of the vascular space is increased by the adrenergic blockade. A combination of hydrocortisone, phenoxybenzamine, and plasma may be the best regime of all.

Block et al. (1966) reported that administration of steroids such as corticosteroids show a dose response and have an effect on regional blood flow in the shocked dog resembling the pattern observed with α adrenergic blockade (Lillehei et al., 1964).

Massive doses of corticosteroid have little or no relation to the physiological effects of adrenal glucocorticoids but are pharmacological agents capable of lowering peripheral resistance, particularly within the viscera (Moses et al., 1965). The primary beneficial effects of glucocorti-

coids in shock may rest as much on their ability to maintain the integrity of cell membranes and subcellular particles, mitochondria, and lysosomes as upon their ability to influence the dynamics of the circulation (Lillehei et al., 1964).

Perlroth and Harrison (1969) reported that corticosteroids are specific for the treatment of shock when it is due to adrenal insufficiency. Topel (1968b) reported that adrenal cortical steroids are associated with stress adaptation. It is only when an animal is stressed that survival depends on the presence of the cortical steroids, and their influence on stress adaptation is associated with circulatory homeostasis. It appears that muscular fatigue from stress in an adrenal insufficient animal is not due to an impaired musculature or myoneural junction but to a circulatory collapse (Ramey and Goldstein, 1957). When an animal is stressed, epinephrine produces a shift of blood flow from the splanchnic area to the working muscle (Ramey et al., 1951). In the absence of adrenal cortical steroids, the threshold for epinephrine and norepinephrine action is greatly raised, and therefore, when an adrenal insufficient animal is stressed, splanchnic engorgement occurs due to the abnormal shift of blood from the splanchnic region to the skeletal muscle, and a vascular collapse occurs (Ramey and Goldstein, 1957).

It appears that the adrenal insufficient animal attempts to compensate for the lack of effective effector-organ response to sympathetic stimulation by increased activity within this system (Sheehan, 1948). The high titre of constrictor materials released ultimately acts to destroy the responsiveness of the small blood vessels. Administration of steroids up to a certain point will protect the effector organs against these influ-

ences (Fritz and Levine, 1951; Ramey et al., 1951), but even the intact animal with a functional adrenal cortex finally succumbs to excessive sympathetic bombardment (Overman and Wong, 1947; Wiggers et al., 1948; Topel et al., 1968). Further addition of steroids at this point is virtually useless in preventing death (Lewis and Freytag, 1951; Topel et al., 1968).

Shayer (1963) indicated that increased output of glucocorticoids during stress balances the effects of increased rate of induced histamine by affecting potentiation of pressor effects by adrenal steroids. This is characteristic of corticoid-epinephrine interaction in all stressful situations (Ramey and Goldstein, 1957). The signs reported for the porcine stress syndrome (Topel et al., 1968) show evidence of circulatory disorder, and it appears that pigs undergoing this syndrome lack the ability to secrete adrenal glucocorticoids during stress (Topel, 1968b). Therefore, these individuals have difficulty removing or metabolizing lactic acid due to a circulatory disorder.

Ludvigsen (1957) stated hypofunction of the thyroid and adrenal cortex as the cause of muscular changes similar to those of PSE pork. Observations of stress susceptible and control pigs before and after a ten-minute stress period led to the conclusion that a reduced level of thyroid hormone in the blood and a lowered ACTH content of the anterior pituatary gland contributed to the incidence of PSE musculature.

Henry et al. (1958) and Judge et al. (1966, 1968) indicated a deficiency of glucocorticoids in stress susceptible animals. Mean values of 17-ketosteroids found in 24-hour urine samples tended to be lower, plasma protein bound iodine (PBI) higher, and thyroid ^{131}I uptake lower in stress type than in stress resistant pigs. Topel et al. (1967) reported plasma

17-OHCS levels from pigs possessing severe PSE muscle 3.3 µg per 100 ml lower than the dark, firm and dry group. Ludvigsen (1968) reported exogenous administration of synthetic cortical steroids (nordisolone) allowed stress susceptible pigs to adapt to heat exposure.

Nichols and Tyler (1967) reported exogenously administered glucocorticoids can suppress ACTH release and cortisol synthesis, and when given in sufficiently large doses, cortisol synthesis may be blocked. Marple (1968) reported the blocking of cortisol synthesis with prednisolone, substantiating Nichols and Tyler (1967).

No significant correlation was found between adrenal weight and plasma 17-OHCS levels (Topel et al., 1967) or porcine muscle morphology or muscle pH (Addis et al., 1965). Marple (1968) found plasma 17-OHCS levels significantly correlated with adrenal weights of the control group.

Cassens et al. (1965) observed the adrenocortical lipid content of the zona reticularis and found that adrenal glands from stress prone pigs possessed a greater concentration of lipid masses. Cassens et al. (1965) suggested that the increased lipid masses may represent a degenerative change in the adrenal cortex and thus provide a reason for the apparent reduction of urinary 17-OHCS concentration of the stress prone pig. These authors also indicated that the reported changes in the zona reticularis may be associated with a rapid post-mortem pH decline in muscle.

Glenn et al. (1961) and White et al. (1968) concluded that hydrocortisone influences the metabolism of glucose at a level at which pyruvate or lactate plays a predominant role and that hydrocortisone markedly influenced the conversion of lactate to glycogen. Altura (1966) found that glucocorticoids (cortisone, prednisolone, or dexamethasone), when administered

systemically to normal rats, produced no observable changes in the diameters of the muscular microvessels over a period of two hours. However, glucocorticoids increased the vascular reactivity to constrictor catecholamines, while histamine induced vasodilation was suppressed. It was concluded that glucocorticoids function in the local regulation of blood flow via the response of vascular smooth muscle to other endogenous humoral agents.

Glucocorticoids are also believed to function by moderating the actions of the intrinsic dilator, histamine, which has been suggested as being responsible for the control of microcirculatory dilation rather than carbon dioxide, oxygen deficiency, lactic acid, and pH changes (Shagal and Shraiberg, 1964).

Analysis of cortisol

Soffer et al. (1961) defined corticoids as steroids present in the adrenal cortex possessing 21 carbon atoms and three or more oxygen atoms. Murphy (1967a) reported that chemical analysis of adrenal venous blood showed that glucocorticoids, cortisol, and corticosterone are quantitatively the most important steroids. This author stated that unconjugated plasma cortisol (hydrocortisone) was a useful measure in peripheral blood of adrenocortical activity.

Murphy (1967a) further reported that two-thirds of the corticoids were unconjugated, and one-third were conjugated to glucuronides and sulfates. The unconjugated corticoids, which are usually measured, comprise a fraction nine-tenths of which are bound to serum proteins (corticosteroid-

binding globulin-CBG and transcortin-and albumin) and an unbound or native or one-tenth ultrafiltrable fraction.

Most techniques involve: 1) solvent extraction of plasma, 2) purification of the crude extract, and 3) identification and quantitative determination. Both protein-bound and unbound forms are measured since all the extraction procedures employed remove the steroids from the proteins (Murphy, 1967a).

Extraction of cortisol and corticosterone is accomplished with an organic solvent and then followed by further purification (Murphy, 1967a). Braunsberg and James (1961) concluded that for cortisol and cortisone, methylene chloride and ethyl acetate are the solvents of choice and that chloroform may be equally satisfactory. Murphy (1967b) reported that heat and alcohol could also be used to destroy the binding proteins that may otherwise act in the same way as the assay protein.

The competitive protein-binding analysis consists of two parts: first, the deproteinization of the plasma - to remove or destroy the CBG present, and, secondly, the quantitation of the corticosteroids in the deproteinized plasma. This is accomplished by equilibrating the deproteinized plasma with a solution containing CBG saturated with radioactive cortisol, then separating and counting the protein-bound fraction. The unlabeled cortisol competes with the tracer cortisol for the binding sites on the CBG molecules, displacing some of them, so that the amount of radiocortisol in the portein-bound fraction is inversely proportional to the amount of unlabeled cortisol added in the sample (Murphy, 1967a).

Thus, conditions are chosen so that the CBG of the solution is just saturated with the tracer steroid. Since the steroid bound to the CBG is

in dynamic equilibrium with the unbound steroid, the steroid of the sample displaces a portion of the tracer, and the measured percentage of tracer bound to the CBG falls proportionately. The protein-bound and unbound fractions are then separated, and the distribution of the tracer is determined. The steroid of the sample is quantitated by comparing its displacement of tracer with that caused by known amounts of the same steroid (Murphy, 1967b).

The quantitation step involves two parts (Murphy, 1967b). Equilibration with tracer and assay of protein involves sample steroid displacement of tracer from the assay protein in proportion to the amount present. This is accomplished at room temperature followed by cooling to $10^{o}C$ or lower-binding capacity varies with temperature.

The second part of the quantitation step involves separation of protein-bound and unbound steroids allowing one or both fractions to be counted. This can be accomplished by dialysis, electrophoresis, gel filtration, ion exchange resins, protein precipitation, and adsorption of the unbound fraction to insoluble particles such as the aluminum silicates - Fuller's Earth and Lloyd's reagent, the magnesium silicate - Florisil, and coated charcoal.

Fuller's Earth, coated charcoal, and Lloyd's reagent were found suitable for separating protein-bound and unbound cortisol (Murphy, 1967b). This author found Florisil and coated charcoal suitable for separating protein-bound and unbound corticosterone. Uptake by the silicates was somewhat decreased at higher temperatures with greater sensitivity seen with less CBG. For all four adsorbents, there was an increase in the amount of

^{3}H-cortisol bound by the adsorbent as the temperature increased. CBG is known to bind steroids more avidly at lower temperatures (Murphy, 1967b).

Longer shaking time increased the uptake by the adsorbents. If the samples were allowed to stand for various lengths of time over a ten-minute period after shaking, there was no change in the amount taken up by Florisil, which quickly settles to the bottom of the test tube. There was a significant change observed with Fuller's Earth, Lloyd's reagent, and especially coated charcoal, which remained suspended until centrifuged. After centrifugation, no further change occurred (Murphy, 1967b).

In the assay, standards were included with every group of samples so that differences in adsorbent uptake from one run to another did not offset the results obtained. Murphy (1967b) found for any given plasma concentration, under fixed conditions of shaking, the greater the amount of adsorbent added, the greater the amount of steroid taken up by it. This author found Fuller's Earth used with ^{3}H cortisol as a tracer provided a system with increased specificity for cortisol.

According to Murphy (1967b), the steroid of the sample is quantitated by comparing its displacement of tracer with that caused by known amounts of the same steroid. If the percentage of bound tracer is plotted against the amount of steroid added, a curve may be drawn. If the reciprocal of the percent bound steroid is used, a straight line relationship is obtained over the usable range. Since the time required to count the protein-bound fraction to a preset number of counts is proportional to the reciprocal of the percent bound steroid, it is more convenient to plot the time required to reach a preset count vs. the amount of steroid added, since no calcula-

tions are necessary. The data presented in this dissertation was obtained by plotting activity as time to 10,000 counts vs. steroid concentration.

Murphy et al. (1963) and Murphy (1967a) found a definite diurnal variation in cortical steroids, as was also reported by Weiss et al. (1970). All of these authors reported higher circulatory levels during morning sample collection comprising the time period of 6:00 A.M. to 9:00 A.M., followed by a decline in basal levels as the time of day progressed.

Seal and Doe (1963) and Lindner (1964) investigated plasma corticoid binding in a variety of species and suggest that plasma level and biological half-life of cortisol in different species are directly related to binding capacity. Mlynaryk et al. (1962) reported that although plasma corticoid levels tend to be low, urinary 17-OHCS and cortisol production rates are significantly elevated in obese as compared with normal subjects.

Murphy et al. (1963) indicated that neither hemolysis nor heparin impaired the specificity of the protein-binding assay technique.

Murphy (1967a) stated that urine collections are cumbersome to handle and often incomplete. Metabolic excretion is altered in hepatic and renal disease and in obesity. In contrast, blood samples measure the active hormones and are more easily collected. This logical reasoning, to a major degree, influenced the decision of analyzing cortisol and epinephrine in the study reported in this dissertation through the technique of blood collection and plasma assay.

Alpha (α) and Beta (β) Blockade

Previous mention has been made within the body of this literature review to endocrine influence upon and reaction with α and β receptors.

Norepinephrine has been attributed to react with α receptors resulting in vasoconstriction, iris dilation, pilomotor contraction, and intestinal relaxation. β receptors are held responsible for vasodilation in muscle, increased myocardial contractile force, and bronchial relaxation (Dietzman et al., 1967). The sympathoadrenal stress response is greatest in the vasoactive, adrenergically sensitive viscera and skin, and the α receptors in these areas are sensitive to the outpouring of catecholamines.

Theoretically, survival should be improved by the reestablishment of equitable blood flow to all tissues. Practically, this can be accomplished by the administration of vasodilating agents in combination with volume replacement. Reduction of vasoconstriction can be accomplished by: reduction of the effects of sympathetic nerve stimulation (α adrenergic blockade with phenoxybenzamine), β adrenergic stimulation with isoproterenol, an undefined mechanism with massive doses of adrenal corticosteroids, and saturation of the sympathetic nervous system with epinephrine, which reduces the vasoconstrictive response of sympathetic stimulation (Dietzman et al., 1967).

Pharmacological blockade of sympathetic vasoconstriction lowers total peripheral resistance, redistributes blood to ischemic viscera, and increases vascular capacitance (Lillehei et al., 1965; Vick et al., 1965). The catecholamines reinforce the action of locally released neurotransmitters. α block effects can be summarized as follows: 1) long periods of relatively complete blocking-phenoxybenzamine, 2) significant blockade but usually partial and transient-phentolamine, tolazoline, and azopetine, 3) short acting partial blockade-piperoxan, and 4) no significant blockade in man-ergot alkoloids (Block et al., 1966).

Phenoxybenzamine produces specific and persistent blockade of α receptors which are found in greatest concentration in visceral and cutaneous vascular smooth muscle. Even when used in much larger doses than required to exert a maximum blocking effect, phenoxybenzamine still produces no inhibition of the inotropic cardiac response to catecholamines although it completely blocks their peripheral effects. Conversely receptor agents have little blocking effect on adrenergic vasoconstriction but have pronounced cardiac activity (Block et al., 1966).

α adrenergic blockade is effective on both the arteriolar and venular sides of the microcirculation. The small venules of the body are potentially the major capacitance vessels. During the phase of stagnant microcirculatory anoxia associated with sustained sympathetic vasoconstriction, there appears to be increased capacitance in the dilated acidotic engorged capillary beds of the microcirculation rather than in venules that are constricted (Lewis and Mellander, 1962). Along with producing arteriolar relaxation, phenoxybenzamine induces loss of venular tone, thus reducing capillary hydrostatic pressure and enlarging the venular capacitance. Therefore, phenoxybenzamine administration needs to be accomplished with volume replacement.

Phenoxybenzamine is a moderately potent antihistamine and antiserotonin (Nickerson, 1963), blocks the release of ferritin from the liver, and may suppress the release of vasoactive agents (Baez et al., 1958). It plays some role in maintaining integrity of the phagocyte system which may be impaired in shock (Smuddy et al., 1958) and appears to block some of the direct cellular toxic effects of gram-negative bacterial endotoxins (Gourzis et al., 1961). Following phenoxybenzamine administration, the

oliguric or anuria subject in shock usually shows improved renal perfusion of urine flow (Nickerson, 1963), part of which is due to improved splanchnic blood flow, but part may be due to a central nervous system mechanism (Davies et al., 1965). Phenoxybenzamine given to patients suffering from cardiogenic shock and acute pulmonary edema and to dogs with induced pulmonary edema improves pulmonary perfusion and may relieve the edema (Sukhnandan and Thal, 1965).

Phenoxybenzamine without volume replacement can lead to percipitous decline, and death may follow the onset of the blockade. These deaths are characterized by very low cardiac output, severe hypotension, seizures, and respiratory arrests apparently related to poor cerebral perfusion and are not typical of usual forms of shock death (Eckenhoff and Cooperman, 1965). Pretreatment with phenoxybenzamine one to five hours in advance reduces the incidence of shock death but makes rats more susceptible to acute traumatic death.

Catecholamine shock can be produced clinically with infusions for 90-120 minutes. Phenoxybenzamine blockade before pressor infusion in dogs blocks the vasoconstriction effect of catecholamines and prevents the characteristic hypertension and visceral ischemic changes. Administration of steroids (corticosteroid) shows a dose response and has an effect on regional blood flow in the shocked dog resembling the pattern seen with α adrenergic blockade (Lillehei et al., 1964).

Bave et al. (1966) studied the deleterious effects of prolonged sympathetic activity or vasoconstriction in dogs and have suggested the use of vasodilator agents in shock. When phenoxybenzamine was given during hemorrhagic shock, 55 percent of the volume bled out was returned to maintain

the same blood pressure thus giving a quantitative estimate of the increased vascular space. Cardiac output and oxygen consumption increased with the added volume, but improved distribution of flow to the mesenteric circulation did not occur and mesenteric oxygen consumption decreased, suggesting decreased capillary blood flow. Giving phenoxybenzamine, after a period of shock and return of shed blood, decreased vascular resistance but at the expense of marked decreases in cardiac output and regional flow.

According to Perlroth and Harrison (1969), there is a decrease in blood flow during shock conditions, therefore, agents which lower peripheral resistance and increase flow are desirable. α adrenergic blocking agents such as phenoxybenzamine and phentolamine have been used for treatment of septic and other forms of shock (Wilson et al., 1964; Nickerson, 1965; Anderson et al., 1967; Hardaway et al., 1967).

Wilson et al. (1964) studied the use of dibenzyline (Phenoxybenzamine HCL) in humans. Many studies, presented earlier, substantiate that reflex sympathetic vasoconstriction in shock brings about a redistribution of circulation in such a way as to maintain flow preferentially to the heart and brain. While this adjustment is an important adaptation for immediate survival, prolonged vasoconstriction in the remainder of the body, if continued for long periods of time, may cause serious consequences. Dibenzyline, an α receptor blocking agent which abolishes the arteriolar and venous constrictor effects of l-norepinephrine, is a particularly valuable agent for abrogating this vasoconstriction. Remington et al. (1950), Baez et al. (1958), and Nickerson and Carter (1959) have shown that pretreatment of animals with this agent protects against various forms of otherwise fatal experimental shock. Many animal studies and a limited

clinical experience by Nickerson and Gourzis (1962) have substantiated this work. A more extended study by Wilson et al. (1964) involving a larger number of humans confirmed the results observed in animals and on a limited number of clinical cases previously studied.

According to Kayaalp and Kiran (1966), the α adrenergic blocking agents, phentolamine and phenoxybenzamine, reduced or abolished the pressor response to propranolol (a β blocking agent). It did not produce any pressor response in spinal dogs or in dogs whose adrenal glands were excluded from circulation.

The β blocking agent, propranolol HCL (Inderal), is employed in clinical trials. To explain the difference in action of norepinephrine and epinephrine on different sympathetic effector organs, α and β receptors have been postulated to exist. No structure or specific cellular component has so far been identified which might be considered the adrenergic receptor site; it is by the behavior of the effector organ in response to sympathomemetric amines which determines the presence of the α or β receptors. Thus, a β block would diminish heart rate, heart automaticity, and myocardial contractility and may possibly induce bronchospasm. In the intestines, stimulation of both α and β receptors inhibits smooth muscle contraction (Copeland, 1967).

α blockade can be accomplished with ergot alkaloids, phenoxybenzyline (Dibenzyline), etc. Propranolol can induce β blockade at about 1/10 the dose required with pronethelol with no side effects of lightheadedness, slight incoordination, nausea, or vomiting at the effective dose. Copeland (1967) further reported that inderal produces a fall in heart rate, a decrease in cardiac output, a decrease in resting stroke volume, a decrease

in ventricular diastolic and systolic volume, and, therefore, a change in tension of the myocardial wall with oxygen consumption falling by 25 percent. Exercised subjects show a significant decrease in heart rate and systolic blood pressure after propranolol. The most harmful effect of Inderal is intensification of heart failure due to loss of sympathetic support to the failing myocardium.

Propranolol was introduced by Black et al. (1964) as a potent beta adrenergic receptor blocking agent. Long-term treatment caused reductions of blood pressure in hypertensive and normotensive patients (Prichard and Gillam, 1964; Gillman and Prichard, 1965). These authors attributed this effect of propranolol to interference with the function of the sympathetic nerves to the heart. However, propranolol given intra-arterial produced a sustained vasoconstriction in the perfused hind limb of the dog (Nakano and Kusakari (1965 and 1966).

Kayaalp and Kiran (1966) reported that propranolol induced a transient vasodilation by a sustained vasoconstriction in the denervated autoperfused hind limbs of dogs. These authors also found the α adrenergic blocking agents, phentolamine and phenoxybenzamine, reduced or abolished the pressor response to propranolol. They proposed that such results suggest that the pressor response to propranolol is due to the release of catecholamines from the adrenal medulla, which may be related to a reflex activation. Another possibility is that the release of catecholamines by propranolol may have a connection with the central nervous system and require an intact sympathetic flow to the adrenal medulla.

Propranolol has been shown to block the inotropic and chronotropic responses produced by the intravenous administration of isoprenaline,

adrenaline, and noradrenaline in anesthetized dogs (Shanks, 1966). The vasodepressor action of isoprenaline was abolished and the pressor response to adrenaline potentiated. The latter effects were attributed to blockade of the peripheral vasodilator actions of isoprenaline and adrenaline which occur to a large extent in the vascular bed of skeletal muscle (Whelan, 1952; Bowman, 1959; Green and Kepchar, 1959; Whelan and de la Lande, 1963).

Shanks (1967) found intra-arterial infused propranolol produced a transient vasodilation which was dose dependent. Propranolol was found to be at least ten times more effective than its (+) isomer in abolishing the vasodilator action of isoprenaline. Propranolol also blocked the vasodilation produced by adrenaline and potentiated its vasoconstriction effect. The vasodilation in response to adrenaline and noradrenaline after phenoxybenzamine treatment was inhibited by propranolol.

Black et al. (1964) showed that propranolol produced a decrease in externally measured indices of myocardial mechanical effort and, consequantly, a fall in myocardial oxygen demands. Propranol produced different changes in myocardial arteriovenous oxygen extraction depending upon whether the coronary circulation was normal or diseased. β adrenergic blockade caused a decline in cardiac filling pressures and volumes at the dose level of 5 mg in humans (Wolfson and Gorlin, 1969), presumably by decreasing venous return.

It is now well established that propranolol decreases many of the measurable external parameters of myocardial effort such as heart rate, cardiac output, and external left ventricular work. Concomitant with these changes, coronary flow and myocardial oxygen consumption have been shown in man to be reduced below control values (Wolfson et al., 1966).

Berne (1958) has shown a biphasic change in coronary flow when norepinephrine and epinephrine are infused directly into coronary arteries in dogs. An initial decrease followed by a prolonged increase in coronary blood flow was seen, the latter phase being associated with an increased arterial-venous oxygen difference. Similar results were found using isoproterenol, both phases being abolished by β blockade.

Hypertension has long been ascribed to increased peripheral resistance (Page and McCubbin, 1956); therefore, its treatment has been primarily directed toward blood pressure reduction by decreasing vascular resistance. β adrenergic receptor stimulation results in peripheral vasodilation, and β adrenergic inhibition also reduces cardiac output (Ulrych et al., 1968), another hemodynamic variable directly affecting arterial pressure.

Elevated arterial pressure in hypotension has been ascribed to increased peripheral resistance since cardiac output is normal (Freis, 1960). Since β adrenergic receptor stimulation produces peripheral vasodilation, increased heart rate, and myocardial contractility, inhibition of β receptors should, therefore, increase vascular resistance and decrease cardiac output. Ulrych et al. (1968) infused intravenously the β blocking agent, propranolol, into six normal subjects and 21 hypertensive patients. Arterial pressure was not reduced, but cardiac output fell by approximately 20 percent in both groups. Nevertheless, beta adrenergic inhibition seemed to have different effects on the two groups; propranolol produced a greater inhibition of chronotropic activity in hypertensive patients and greater inhibition of stroke volume in the normotensive individuals whose pretreatment heart rate was slower than that of the hypertensive patients.

Berk (1970) concluded that β blockade with propranolol is effective in the treatment of hyperdynamic shock in man, such as septic shock. Cohn (1966) reported that isoproterenol is a potent inotropic agent which produces vasodilation rather than vasoconstriction. It alleviates the shock condition by increasing heart rate and cardiac output and reduces peripheral vascular resistance.

Kern et al. (1968) reported significant depressions in ventricular contractility of dogs at pH 7.1 and pH 6.8, but the depressions were preceded by transient positive inotropic changes. Dogs pretreated with propranolol showed no positive effects, and their final decreases in left ventricular function were more severe. THAM infusions returned pH to control levels and increased contractility in all dogs. Therefore, acute lactate acidosis affects ventricular function through: 1) direct depression, 2) catecholamine release, and 3) reduction of ventricular responsiveness to catecholamines.

Metabolic Parameters, PO_2, and pH Associated with Stress and Shock

Metabolic substances can also influence the micro-circulatory bed of skeletal muscle. Anoxia increases the CO_2 tension, lactate levels, H^+, and ATP concentrations, and these chemical components have been reported as the local determinants eliciting skeletal muscle vasodilation during exercise (Best and Taylor, 1961; Nahas and Payart, 1967; Skinner and Powell, 1967). Anoxia and high blood lactate values lead to adrenal cortical activation (Stickney and Van Liere, 1953; Topel, 1968a), and under these circumstances, an increase in adrenal steroids is necessary for circulatory homeostasis and to maintain life (Thorn et al., 1945). The adrenal insufficient animal

is more susceptible to anoxia (Thorn et al., 1945), and a very high content of lactic acid develops in the plasma and muscle after exercise (Marple et al., 1969) resulting in death for extreme individuals. Death from acute anoxia or acidosis reveals that the fall in blood pressure may be due to the diminished constrictor action of various hormones, the absence of adequate oxygen, or a low blood pH. Also, epinephrine and probably norepinephrine don't have a normal pressor effect (Shurtshin et al., 1948; Van Loos et al., 1948; Nahas and Payart, 1967).

Lillehei et al. (1964) observed that there is always a lowering of blood pH as shock progresses although these authors stated that this shift does not appear to have prognostic significance. These researchers did suggest that events leading to the irreversible state are initiated with the spasm which affects both venules and arterioles and results in an ischemic capillary bed. As the shock is prolonged, the continued ischemia results in relaxation or loss of tone of the precapillary sphincters (resistance vessels). This relaxation is probably a consequence of ischemia and local acidosis in the surrounding tissues.

Payart and Nahas (1966) studied the calorigenic and metabolic effects of norepinephrine and epinephrine in young Beagles. Both norepinephrine and epinephrine increased oxygen consumption to the same extent at normal pH. During hypercapnic acidosis, this calorigenic effect of epinephrine and norepinephrine was inhibited. Hyperglycemia responses to catecholamine infusion were not changed by acidosis. An increase in H^+ concentration exerts antagonistic effects on catecholamines stimulating their release and at the same time inhibiting their metabolic effects.

Schumer and Sperling (1968) defined shock as a molecular disease proposing that the metabolic derangements associated with shock revolve around anaerobic metabolism, which produces increased amounts of lactate, amino acids, fatty acids, and phosphoric acids. Metabolic acidemia produces lysosome membrane disruption with the outpouring of the lytic enzymes causing death of the cell. Associated with this anaerobic metabolism is a decreased production of the energy component ATP. This causes a derangement of protein synthesis and cell membrane pump function. These authors further propose that the derangement of protein synthesis reduces the ability of the organism to combat shock, and the cell membrane pump function derangement produces cellular edema and mitochondrial edema.

According to Wilkens et al. (1970), the ability of the microvascular system to respond to the ever changing metabolic needs of the various tissues is a fundamental requirement for maintaining homeostasis. Vasodilation following a lowering of blood pH has been demonstrated early in scientific investigation and confirmed by many (Krogh, 1929; Fleisch et al., 1932; Kester et al., 1952; Zsoter et al., 1961; Molnar et al., 1962). It has been substantiated that muscular activity is accompanied by a decreased pH of the effluent venous blood (Kontos and Patterson, 1964; Ross et al., 1964; Rudko and Haddy, 1965; Kontos et al., 1966). Evidence suggests that a decrease in the pH of the blood and tissue fluids, such as occur during increased metabolic activity or during under perfusion (Frey, 1930; Kontos et al., 1965; Kilburn, 1966; Kontos et al., 1966; Bergan et al., 1967), may represent a stimulus capable of activating the major biological systems concerned with blood coagulation, fibrinolysis, and kinin formation.

The potential significance of such pH mediated release of kinins must be viewed in light of the potent pharmacologic properties of kinins. Nanogram quantities of these potent polypeptides suffice to effect a pronounced degree of vasodilation and a proportionate increase of blood flow in a variety of vascular beds (Fox et al., 1961; Maxwell et al., 1962; Paldino et al., 1962; Kontos et al., 1964). All these considerations and the important fact that kinins are rapidly destroyed by kininases (Erdos, 1963), present in both plasma and tissue fluids, have suggested the possibility that a pH-mediated release of kinin might very well represent a decisive link within a metabolically controlled biochemical mechanism or peripheral vascular autoregulation. Wilkins et al. (1970) state that kinins may play a secondary role wherein tissue hypoxia, produced by extensive hemorrhage or a great variety of other causes, may act as the initiating event followed by the activation of the kinin and related biochemical systems.

The increase in lactate and pyruvate content of arterial blood during experimental and clinical states of shock and the extent to which such increases serve as measures of oxygen deficit and irreversible injury were investigated by Weil and Abdelmonen (1970). Induced hemorrhagic shock in the rat during a four-hour bleeding period saw oxygen consumption decrease 40 percent, pH change from 7.39 to 7.08, an increase in lactate from 0.80 mM to 6.60 mM, and a pyruvate increase from 0.07 mM to 0.18 mM. Analysis of the data showed lactate to serve as a sensitive predictor in clinical cases for survival i.e., as lactate increased from 2.1 mM to 8.0 mM, the estimated probability of survival decreased from 90 to ten percent.

Experimentally, the reduction in oxygen consumption during shock is predictably related to survival (Crowell and Smith, 1964). According to Huckabee (1958), Broder and Weil (1964), and Peretz et al. (1965), current techniques of gas collection for measurement under controlled conditions prior to the onset of shock are rarely available; the measure itself is technically difficult, and, therefore, investigators have sought indirect measures of oxygen consumption or oxygen deficit i.e., lactate and pyruvate. Huckabee (1958b) and Schumer (1968) stated that circulatory anoxia accounts for the accumulation of lactate and in part for the progressive acidosis characteristic of shock-aerobic oxidation in the TCA cycle is blocked. The oxidation of $NADH_2$ to NAD is controlled by the lack of oxygen. The buildup of NAD in the presence of LDH shifts the equilibrium to the reaction favoring lactate accumulation.

Measurement of the maximum ability of the circulatory system to transport oxygen during a period of hypotension shows that oxygen becomes "flow limited", and only approximately 50 percent of the body needs are met at a hypotensive pressure of 30 mm Hg (Crowell, 1970). This author proposed that the decreased metabolism associated with hypotension is, therefore, related to inadequate oxygen supply and not due to decreased demand. The destruction of the body tissues is related to the internal distribution of this inadequate supply of oxygen and varies from specie to specie, as well as from other factors such as the experimental method of producing shock.

After producing irreversible shock (Crowell, 1970), pathological lesions were observed in the heart, lungs, liver, kidney, and other areas. While the heart showed the most extensive damage, it is clear that different experimental methods of producing shock may alter the "target organ".

Hypotension is a condition of total body ischemia and hypoxia (Crowell, 1970). This author further stated that tissues are damaged, some extensively and sufficiently to be fatal. Death from the damage may be immediate or delayed. The declining pressure may be due to cardiac damage, fluid loss, or both, but death may be caused by either (Crowell, 1970).

Rothe (1968) stated that although oxygen deficits in certain vital tissues may be crucial to ultimate survival, cumulative total oxygen defi-cet is not an adequate measure of this deficiency. With regard to smooth muscle, Detar and Bohr (1968) observed that oxygen tension is an important determinant of contractile tension developed by isolated helical strips of rabbit aorta. A decrease in oxygen pressure below 10 mm Hg causes the contractile response of epinephrine to diminish linearly. The immediate dependence of contractile tension on the partial pressure of oxygen is explained on the assumption that oxygen plays a metabolic role within the mitochondria of the smooth muscle cells as the final electron acceptor in the respiratory chain.

Influence of pH and Lactate on Muscle Characteristics

A positive correlation has been shown to exist between water holding capacity, muscle color intensity, and pH (Bate-Smith, 1948; Lawrie, 1958; Briskey, 1959; Wismer-Pedersen, 1959; Briskey et al., 1960; Judge et al., 1968). These researchers determined that dark, firm muscle was higher in pH and lower in free water than pale, soft muscle. Briskey and Wismer-Pedersen (1961) observed continuous pH and temperature changes during post-mortem chilling. Carcasses that had a rapid, significant pH decrease to 5.1, 1½ hours post-mortem possessed pale, exudative, soft tissue. In con-

trast, rapid chilling of the muscle before 45 minutes post-mortem prevented the development of PSE muscle.

Sayre et al. (1964) concluded that onset of rigor mortis was important in the development of PSE muscle. When onset of rigor mortis occurred at pH values below 5.9 with temperatures above 35°C, the M. longissimus became pale and watery. However, if onset of rigor mortis occurred when pH values remained above pH 6.0, then the muscle was dark and firm.

Wismer-Pedersen and Briskey (1961) concluded the difference in rate of pH fall was due to a difference in rate of anaerobic glycolysis as illustrated by glycogen and lactic acid determinations. Gunther and Schweiger (1966) reported it was not always possible to associate lactate values and muscle pH at the same post-mortem time. A positive correlation was infrequently found, thus the authors concluded that lactic acid produced by post-mortem glycolysis may not be the only compound responsible for decreasing the pH values in muscle.

Kastenschmidt and Briskey (1966) concluded that higher levels of lactic acid in muscles having a rapid rate of post-mortem glycolysis supported the concept of an oxygen debt prior to death. It was observed that the accumulation of lactate in muscle undergoing rapid glycolysis was nearly complete within 30 minutes post-mortem, while lactate continued to be produced for 180 minutes after death in muscle with slow glycolysis.

Muscle Color and Associated Metabolites

The color observed in muscle tissue is due in part to a protein pigment designated as myoglobin. Schweigert (1956) described myoglobin as a conjugated protein that contains a heme moeity (iron containing porphyrin

gel) attached to the protein, globin. Its function in the live animal is to accept oxygen from the hemoglobin of the blood for use in oxidative energy yielding reactions in the cell. This author found concentration to vary between and within muscles. The heme portion gives rise to the color of myoglobin, although the attachment to the protein (globin) or other constituents, which are in themselves colorless, modifies the color considerably.

Hart (1961) described a method which measured the extinction value of the meat extract. This author stated that the color difference observed by the eye between the meat of different species of animals, between different muscle groups of the same animal, and those between degenerated and normal muscle tissue can in this manner be indicated by a definite number.

The brightness reflected from the surface of muscle to a mechanical observation and recording apparatus has been the underlying principle of color measurement methods developed and employed by Lohse and Pfau (1964), Schroder et al. (1965), and Steinhauf et al. (1966).

Haas and Bratzler (1965) determined oxygenation rates by use of Munsell disk colorimetry and by the Gardner automatic color difference meter. From the data obtained, recommendations can be made for the time to read color as a prediction of total color change due to oxygenation.

Briskey (1959) classified hams into four groups: 1) pale, two-toned, 2) two-toned, 3) normal, and 4) dark. He concluded the individual ham muscles may be distinguished from one another on the basis of physical and chemical characteristics. The light muscles may be distinguished from the adjacent dark muscle in the following ways: lower pH, greater water release, and lower myoglobin content. Briskey et al. (1960), in a study of

ham musculature, found the muscles which exhibited relatively high ultimate pH values showed lower initial glycogen accumulations and greater myoglobin concentrations.

Albertson (1963) stated "muscular degeneration" (MD) was thought to be hereditary, leading to a deterioration in meat color and quality in Danish Landrace pigs. Further work resulted in the thought that (MD) is mainly due to low myoglobin concentration which causes nervous tension and intensified glycolysis, which lead to post-mortem changes in meat quality. It is suggested that the term "muscular degeneration" should be replaced by "myoglobin disease". However, Marple (1968) supports the work of Briskey et al. (1960) reporting that PSE muscle color can develop and have normal myoglobin concentrations.

Wismer-Pedersen (1959) subjectively scored loins for color after they were first grouped on hematin content; then each group was split into subgroups of loins with loose water-weight in mg/g of meat - (LW) numbers below and above 460, respectively. Loins with LW numbers below 460 obtained color scores of 2.5-3.0 (desirable red color) irrespective of the pigment concentration. For loins with LW numbers above 460, the average color score for the two groups with low hematin concentration was about 1.5 (pale color). It was concluded that meat with normal water holding capacity may have desirable color even at lower pigment concentration.

Hamm (1960) suggested that meat color may be influenced by muscle hydration and the structure of the muscle. He stated that the higher the muscle is hydrated, the more "close" is the structure and the lower is the rate of diffusion of oxygen to the intracellular proteins.

McLaughlin and Goldspink (1963) and Goldspink and McLaughlin (1964) showed that holding sarcoplasmic protein extracts above 30°C caused considerable precipitation. The amount of protein precipitated and color observed proved to be an inverse relationship. From their observations, they concluded that the combined effects of high temperature and low pH caused sarcoplasmic protein precipitation and thereby masking of the color of muscle myoglobin.

Energy Metabolism in Relation to Stress and Shock Conditions

Glenn et al. (1963) reported that adrenocortical steroids alter the rates of metabolism of amino acids, proteins, and fat primarily by exerting inhibitory effects on glucose metabolism. Their anti-inflammatory, general metabolic, and direct effects on adipose tissue appear to be directly related to inhibition of glucose metabolism. Generally direct effects of adrenocortical steroids on cells are inhibitory and appear to be related to their ability to alter rates of synthesis of high energy compounds for synthetic purposes. Secondary metabolic effects of exogenously administered adrenocortical steroids can be prevented by administration of glucose. This indirectly influences amino acid metabolism, fat metabolism, increased plasma triglyceride synthesis, and increased carbon dioxide production. Primary effects i.e., increased plasma and urinary glucose and glycogen concentrations are accelerated or markedly inhanced by glucose injection.

Youmans (1967) reported that fatigue would be brought about when there is exhaustion of substrates needed for the chemical reactions concerned with muscular contraction. As a result of accumulation of metabolites during fatigue, fatigue itself is accentuated when blood supply is restricted.

According to White et al. (1968), glucose acts as the initial precursor of major energy metabolic pathways leading to energy rich compounds composed of high energy phosphates. Metabolites of these various pathways accumulate in the ultimate form of lactate and pyruvate, thus providing H^+ ions. Biological buffering systems, especially via carbonate, normally neutralize the excess acids, however, excess metabolites will accumulate during exercise, fatigue, and stress.

Glenn et al. (1961) reported the injection of glucose or lactate markedly influenced the glycemic response of hydrocortisone. The increases in muscle glycogen synthesis after hydrocortisone injections were less than those that occur in the liver and did not occur unless large amounts of glucose were also injected. It was found in adrenalectomized fasted rats that hydrocortisone increased the production or availability of lactic acid and that lactic acid administered alone led to an increase in net glycogen synthesis. Glenn et al. (1961) and White et al. (1968) concluded that hydrocortisone influences the metabolism of glucose at a level at which pyruvate or lactate plays a predominant role and that hydrocortisone markedly influenced the conversion of lactate to glycogen.

Dhar et al. (1967) and Dutta and Dhar (1968) reported that severity of anaphylactic shock is altered by varying the level of glucose in the blood. It was shown that when hypoglycemia was induced by injection of insulin before physical challenge, systemic anaphylatic shock was potentiated in rats, mice, guinea pigs, and rabbits. Dhar (1970) reported that when animals were made hyperglycemic either by alloxan pretreatment or by hypertonic glucose infusion, the systemic anaphylatic shock was markedly reduced in the rat, mouse, and rabbit. Glucose infusion either abolished or reduced

the degree to which blood pressure decreased during anaphylatic shock in dogs (Dhar, 1970). This researcher proposed: 1) anaphylatic shock is potentiated by hypoglycaemia and prevented by hyperglycemia. However, there is a species variation, 2) the mechanism of protective effect is still obscure though reduced resistance to histamine might be a contributing factor, 3) hypoglycemia is associated with antigenic sensitization. β adrenergic blockade which also produces hypoglycemia may be an associated factor, 4) antigenic sensitization produces hypoglycemia after ten days in rats and mice. In the guinea pig, the rabbit, and dog, under similar conditions, hypoglycemia occurs 20 days after injection of an antigen.

Scrutton and Utter (1968) reported with reference to the liver that regulation of the glycolytic flux by substrate availability and metabolic effectors may be the primary control mechanism since the observed flux is considerably lower than the maximal catalytic capacities of the unique glycolytic enzymes of this organ.

Schumer (1968) hypothesized a specific location of the energy pathway block in shock. According to this author, proteins and fats can enter the energy production pathway at strategic steps but must pass through the glycolytic and oxidative cycles for oxidation releasing energy which is then absorbed by coenzymes. These coenzymes carry the energy to respiratory enzyme pathways for incorporation in the high-energy phosphate bonds of adenosine triphosphate. The disadvantages in this system are its oxygen dependency and a common metabolic pathway. An anoxic block to the common metabolic pathway theoretically dooms any protracted energy formation. The role of anaerobiosis in decreasing energy formation is now well accepted. However, the localization and extent of the anoxia block in shock condi-

tions have not been established. Schumer (1968) stated that the first oxidative reaction occurring in the energy pathways is at the pyruvate-acetyl CoA step. This reaction allows entrance of trioses in the oxidative TCA cycle in the mitochondrion. Therefore, any inhibitory effect of anoxia should occur here.

Mineral Parameters Associated with Stress and Shock

Lillehei et al. (1964) stated there are quite marked shifts in electrolytes during hemorrhagic shock experiments. Serum potassium elevations are striking. Furthermore, these researchers found that corrections of the electrolyte imbalance and/or plasma pH drop that always accompanies shock does not change the physiological status of the individual involved. Skinner and Powell (1967) reported that K^+, as well as other metabolites discussed earlier, acts as a local determinant eliciting skeletal muscle vasodilation during exercise.

Sicuteri et al. (1970) reported the most important chemical mediators in myocardial infarction to be 5-hydroxytryptamine, bradykinin, and potassium. 5-hydroxytryptamine does not possess pain producing capacity but is able to sensitize pain receptors to the action of kinins, potassium, and other pain mediators for a long period (Sicuteri et al., 1965; Sicuteri, 1967). These authors reported that serotonin is derived from the degradation of blood platelets, concentrates just below the coronary occlusion, and sensitizes pain receptors to the action of kinins and potassium.

The local effects of ions on cardiac muscle appear important. Perhaps equally important but less well recognized is the ionic ability to alter the contractile state of vascular smooth muscle (Daugherty et al., 1967).

These authors reported that of the major monovalent cations in blood, potassium seems to possess the greatest vasoactivity. A slight increase in potassium concentration of the blood perfusing vascular beds, except perhaps the hepatic system, produces dilation. Increasing blood potassium to high levels produces pronounced constriction of large arteries - lower levels result in dilation limited to mainly small vessels just proximal to the capillaries. Thus, small increases in blood potassium lower total resistance to flow by dilating small vessels, whereas greater elevations raise total resistance because large arteries constrict proportionately greater than small vessels dilate.

These authors further confirmed H^+ to be vasoactive as increases in hydrogen ion concentration results in dilation, and a decrease in concentration leads to constriction with the arterioles acting as the primary site of H^+ effect. No vasoactive sodium effects were observed in this study.

Lefer and Verrier (1970) discussed adrenal gland function in relation to shock with an emphasis on corticosteroids and mineralocorticoids. These authors reported that corticosteroids are of great importance in the regulation of circulatory function, and in their absence, there is circulatory collapse. The predominant feature of the collapse is impairment of myocardial function. Physiologic concentrations of corticosteroids are effective in preventing or reversing the circulatory collapse observed in adrenocortical insufficiency. The relative effectiveness of mineralocorticoids versus glucocorticoids in protecting the circulatory system in adrenal insufficiency has not been conclusively established. Mineralocorticoids exert modest inotropic effects in isolated cardiac tissue; glucocorticosteroids are less effective. In general, pharmacologic concentrations of glucocorti-

coids administered prior to shock increase survival and tend to normalize circulatory function in various forms of shock. Mineralocorticoids do not protect individuals in shock as well as glucocorticoids. Thus, while physiologic concentrations of mineralocorticoids and glucocorticoids can maintain a normal level of circulatory function and compensate entirely for the steroid deficit of adrenal insufficiency, in shock states, pharmacologic effects of glucocorticoids are needed to prevent or moderate the sequelae of the shock state. Mineralocorticoids alone are generally ineffective in preventing shock.

Bohstedt and Grummer (1954) reported a range of 314 to 336 mg percent sodium in pig serum. Widdowson and McCance (1956) reported normal values for serum sodium and potassium of the pig to be 331 ± 10 mg percent and 23.4 ± 2.1 mg percent, respectively. Widdowson and McCance (1950) determined adult swine serum sodium levels to be in the range of 135 to 152 meq/liter; adult chloride levels ranged from 99 to 114 meq/liter. Ullrey et al. (1967) found swine that were five months of age to possess 337 mg/100 ml of serum sodium and serum potassium was determined to be 19.7 mg/100 ml. Weiss et al. (1971) reported 91 kg weight swine to possess 328.8 ± 9.49 mg/100 ml serum sodium, 39.5 ± 2.45 mg/100 ml serum potassium, and 344.2 ± 11.6 mg/100 ml serum chloride.

Hormonal Characteristics of Swine and Their Association with Stress Susceptibility

Research on the response of swine to various stressors has led to the use of terms "stressor susceptible" and "stressor resistant" (Judge et al., 1966; Judge et al., 1967; Judge et al., 1968; Topel et al., 1968). An acute, shocklike, often fatal condition in stress-prone swine has been

described by Topel et al. (1968) and was attributed to an acidosis condition. Similar responses to mild stressors have been described by Ludvigsen (1953 and 1957) who attributed the shock conditions to circulatory insufficiency and hyperthermia. These stress prone animals, suggested to possess insufficient levels of adrenal glucocorticoids, often yield carcasses exhibiting pale, soft, exudative (PSE) musculature (Ludvigsen, 1957; Henry et al., 1958; Judge et al., 1968). Such carcasses have been shown to have high levels of muscle lactate at death and to undergo a rapid rate of post-mortem anaerobic glycolysis (Forrest et al., 1968).

Marple et al. (1969) injected 100 mg prednisolone daily for ten days resulting in atrophy of the adrenal gland. The animals were stressed 48 hours after receiving the last prednisolone injection and then sacrificed. Susceptibility to stress was increased in the adrenal insufficient pigs determined by their inability to withstand five minutes of physical exercise before slaughter. Plasma lactate levels were increased significantly due to the effect of the physical exercise, and blood pH at death was significantly decreased among the stressed, adrenal insufficient group. Initial lactate content of the M. longissimus was significantly lower in the control group; however, no significant difference was obtained among 24-hour muscle lactate values. The glycogen content of the M. longissimus was significantly increased because of prednisolone injections, but the level of initial muscle glycogen did not appear to influence the ultimate amount of lactate produced by post-mortem anaerobic glycolysis. No significant differences were noted among treatments when M. longissimus pH values and color scores were examined statistically. Low levels of plasma 17-OHCS per se did not serve to increase the rate of post-mortem anaerobic glycol-

ysis. These authors proposed that the partial adrenal insufficient swine studied may be unable to adequately remove high levels of lactate from the blood and muscle during exhaustive exercise.

Forrest et al. (1968) reported that "stress susceptible" animals (genetic strain known to have poor heat tolerance) with anesthesia showed significant increases in heart and respiration rates during the first ten minutes of exposure to a warm environment. Further exposure resulted in marked reductions in heart rate and sharp declines in respiration rate. Venous blood PCO_2 increased significantly while PO_2 and pH dropped sharply in "stress-susceptible" animals. Immediately after exsanguination, the skeletal musculature had a low pH and high degree of myolactosis. Esophagial temperature and cardiac outputs increased initially in the "stress susceptible" animals; subsequently, however, the cardiac outputs as well as aortic pressure fell. The "stress resistant" animals (genetic strain known to have good heat tolerance) showed the capacity to maintain physiological homeostasis during exposure to a warm environment.

Judge et al. (1968) reported on pigs incapable of maintaining physiological hemeostasis. When these individuals were subjected to even mild stressors, low PO_2 levels were found in the blood, high levels of lactate in blood and muscle and thus, were categorized as stress-susceptible. Mean values of 17-ketosteroids and 17 OHCS tended to be lower, PBI (protein bound iodine) higher, and thyroid ^{131}I uptake lower in stress susceptible than in stress resistant pigs. Additionally, the PBI levels were more variable in stress susceptible pigs upon their exposure to a warm environment. These authors suggested that these pigs may have some degree of adrenal

insufficiency accompanied by some failure of circulating thyroid hormone to stimulate oxidative metabolism in their straited musculature.

Sybesma and Eckelenboom (1969) reported that very muscular pigs i.e., Piétrains, seem to be highly sensitive to sudden changes in their environment. After intensive exercise, heat development occurs in the musculature and is followed by stiffness of the muscle; this will subsequently lead to death. These authors support the hypothesis of Sybesma and van Logtestyn (1966) that this heat explosion might be due to uncoupling of the oxidative-phosphorylation mechanism in muscle. This hyperthermia is often the main cause of death, according to these authors, since the heart is primarily affected. They suggested the name "malignant hyperthermia syndrome" for the phenomenon.

Steinhauf et al. (1969a) measured 17-OHCS, heart rate, eosinophils, leukocytes, and LDH activity as indicators of stress, as well as post-mortem muscle characteristics. Relation between characters of susceptibility to stress and those of meat quality were found in a few cases. Moreover, the phenotypic correlation between characteristics of susceptibility to stress and those of fattening yield and carcass composition revealed no distinct relations. These authors stated that Selye's theory of the general adaption syndrome does not suffice to explain the lack of adaptation capacity in pigs.

Whipp et al. (1970) measured hydrocortisone concentrations in periph eral blood of swine. Diurnal changes were observed. Minimal concentrations occurred at 4:00 P.M. (0.6 µg/100 ml) and maximum concentrations at 8:00 A.M. (2.4 µg/100 ml). Weiss et al. (1970) also reported diurnal changes in cortisol, lactate, and glucose in swine plasma. Whipp et al.

(1970) stated that the increasing incidence of "production diseases" and the growing interest in the use of swine in biomedical research indicate a need for more information about endocrine, physiological, and biological systems in swine.

Steinhauf et al. (1969b) reported that it is possible to determine the course of reaction to stress by means of repeated blood collection from indwelling catheters. Typical daily rhythms of the examined characters were found. There were considerable fluctuations in the level of the examined criteria between the animals as well as between the different times of investigation. Intensity and kind of reaction to stress are largely independent of intensity and kind of stressor. The rather low capacity of the axis "adrenohypophysis-cortex of the suprarenal gland" in pigs to endure stress cannot be considered the sole cause for the high susceptibility of pigs to environmental influences.

METHODS AND MATERIALS

Experimental Design

Thirty-six swine were managed and fed ad libitum under similar conditions at the Iowa State University Swine Breeding farm. Eighteen individuals were from a fat strain of inbred Poland Chinas (Figure 1) with no history of stress susceptibility or death loss due to the porcine stress syndrome. The remaining 18 were muscular pigs (Figure 1) from sire-dam matings or litters in which a high incidence of stress susceptibility and frequent shock-like death loss occurred. Characteristic muscular, ear, and tail tremors were frequently observed in these pigs, with severe stress resulting in a distinct blotching of the skin, impaired breathing, and inhibition of mobility. These parameters were similar to those reported by Topel et al. (1968) and Weiss et al. (1970). At 95 kg live weight, each pig was isolated into a single pen and catheterized.

Catheterization

One-half hour prior to catheterization, three ml of the tranquilizer, Sparine, were administered to each pig. A Becton and Dickinson (Rutherford, New Jersey) medical grade vinyl .058 ID x .080 O.D. catheter was then inserted into the anterior vena cava at a point directly below the setting of the ear with the aid of a 12 ga. stainless steel needle (Figure 2). Sufficient catheter tubing was forced into the anterior vena cava so that the distal internal end was imbedded in the heart. The needle was then removed leaving the catheter "seated" within the circulatory system. The exterior end of the catheter was then fitted with a plastic tubing adapter (Clay Adams size C-7542) and closed with a two-way stainless steel stopcock

(Becton and Dickinson MS09). The completed adapter-stopcock catheter was then flushed with physiological saline and closed. Sufficient external catheter tubing was allocated to facilitate taping of the terminal end on the dorsal midline midway between the shoulders (Figure 2). A local injection of three ml of antibiotic was administered at the site of catheterization.

Sample Collection

Blood collection via the catheter at 7:30 A.M. and 4:00 P.M. followed catheterization for two days to obtain basal nonstressed samples. Ten ml blood samples were collected for cortisol, epinephrine, glucose, lactate, and electrolyte analysis.

The blood was immediately centrifuged at 500 G for 20 minutes in a refrigerated centrifuge ($4^{o}C$). The plasma was pipetted into screw top glass storage tubes and maintained at $-12^{o}C$ until assayed.

The prescribed times of blood collection and order of sample acquisition were strictly adhered to since diurnal and sampling technique variation were reported by Murphy et al. (1963), Murphy (1967a), and again by Weiss et al. (1970). The swine used in this study developed an accustom to the researcher's presence, and blood samples were frequently obtained from the pigs while they remained in a reclining position. The pigs showed little concern for the person collecting the blood sample.

Administration of the Adrenergic Blocking Agent

The third day after catheterization, the pigs were administered their respective treatments. A total of 12 individuals, six from each strain, received 50 mg per animal of the α block, phenoxybenzamine, 45 minutes

prior to administered stress. Twelve individuals, six from each strain, received 1.5 mg per animal of the β block, propranolol HCl, 20 minutes prior to administration of stress. Twelve swine, six from each strain, received no adrenergic blockade and were designated "within-strain" controls. All infusions were made via the catheter into the venous blood supply. The phenoxybenzamine was diluted to a volume of 500 ml with physiological saline and the propranolol HCl to a volume of 250 ml with physiological saline prior to venous infusion. A 20-minute infusion time was allocated to allow circulatory adjustment to the added exogenous fluid.

A five-minute duration of physical stress was administered to each animal after which blood samples were obtained by following the procedure described earlier. The animals were then sacrificed and an additional blood sample was collected during exsanguination. Both the "stress" and post-mortem blood samples were centrifuged and stored as previously indicated. All glassware and storage tubes were washed with concentrated sulfuric acid and rinsed copiously with deionized water.

Blood pH Determination

Blood pH was determined at each bleeding time. This analysis involved the use of a Corning Blood pH Meter where the temperature of the blood sample was stabilized at 37°C. A KCl reference electrode was used. The blood sample was collected in a 10 cc syringe to prevent exposure to oxygen, and the pH was determined within three minutes after the sample was collected.

M. longissimus Collection

A muscle sample for initial pH and color was removed from the M. longissimus on the left side of the carcass perpendicular to the verte-

bral column at the ninth rib of the unscalded carcass immediately after the animal ceased struggling. A liver sample was obtained at the same time by entering the abdominal cavity. Both samples were immersed in liquid nitrogen and then stored in plastic freezing bags at -12°C for further analysis.

The carcasses were then handled according to conventional processing procedure and placed in a 2°C cooler. A sample of the M. longissimus was also taken at three and 24 hours post-mortem for muscle pH and color analysis.

Determination of Tissue pH and Color

Muscle pH was determined with a Beckman Zeromatic pH meter on a muscle slurry consisting of 10 gm of M. longissimus homogenized in 100 ml deionized water.

M. longissimus color value, a measure of muscle lightness, was determined with a Photovolt 610 Photovolt Reflection Meter. The color intensity was measured as the percent light reflected from the fresh cut muscle surface without allowing the sample to undergo normal oxygenation. The reflectometer was standardized by using an enamel plate with a standard reflectance of 72.5 percent based on magnesium oxide reflectance.

Tissue Sample Preparation

The muscle and liver tissues used in lactate analysis were further frozen in liquid nitrogen, "chipped" into smaller pieces while still frozen, and pulverized for one minute in a Waring Blender which was chilled in liquid nitrogen prior to use. The resulting pulverized samples were placed in freezer bags and without thawing were placed in a freezer at -12°C until analyzed.

Plasma Cortisol (Hydrocortisone) Assay

Cortisol was determined on the plasma obtained from the first ten ml volume of blood withdrawn at each sample collection time. The procedure used coincides with the method reported by Whipp and Lyon (1970). Modification of the assay involved the replacement of the scintillation medium, Bray's solution, with a solution consisting of five gm PPO, 100 cc Biosol #3, and one liter toluene.

Plasma Epinephrine Assay

Epinephrine was determined on the plasma obtained from the second ten ml volume of blood withdrawn at each sample collection time. The analysis was a modification of the trihydroxyindole fluorometric reaction published by Valori et al. (1970).

In the trihydroxyindole (THI) reaction, epinephrine and norepinephrine are oxidized to adrenochrome and noradrenochrome, which are rearranged in alkali to the strongly fluorescent THI derivatives, adrenolutine and noradrenolutine. The fluorescence of the lutines is then stabilized by the addition of an antioxidant which stabilizes the fluorophors and maintains their fluorescence. Ten percent 2,3,-dimercaptopropanol (BAL) in a 25 percent formaldehyde solution was found to be the most beneficial antioxidant by Valori et al. (1970).

The analytical procedure used to obtain the data presented in this dissertation was derived with the use of a Turner Model 111 Fluorometer equipped with a T5 Blue Lamp with maximum light emission of 400-520 mμ. The activation filter was a Primary Filter 405 with 405 mμ passage, and the secondary filter was a Wratten No. 8 Sharp Cut Series with light passage

of 510 mμ. The high sensitivity door was used with a sensitivity setting of 3X.

Standards encompassing the sample epinephrine range were made up in 0.01N HCl with Sigma No. E-4250 L-Epinephrine. Standards were run simultaneously with the samples with the difference in volume between standard volume and plasma volume within the procedure accounted for with deionized distilled water.

All glassware including the cuvettes were washed with concentrated HCl and rinsed seven-eight times with deionized distilled water. No soap of any form was allowed to come in contact with the glassware.

Two and four-tenths ml of clear nonhemolyzed plasma were pipetted into a ten ml test tube. Six-tenths ml of 2/3 M borate, pH 7.0, was added to the test tube to serve as a buffer and to bring the contents to three ml total volume. After addition of 0.15 ml 0.002 percent $CuCl_2 \cdot 2H_2O$, to serve as a metallic catalyst in fluorescence intensity of adrenolutine, oxidation was performed by adding 0.15 ml of 0.25 percent $K_3Fe(CN)_6$. After three minutes, the oxidation was stopped with 0.15 ml of ten percent BAL in a 25 percent formaldehyde solution. This was followed after 20 seconds by addition of 0.6 ml of 10N NaOH to cause molecular rearrangement of adrenochrome to the strongly fluorescent THI derivative, adrenolutine.

Precision of the assay is critically dependent upon timing of the various component additions, order of addition, and accuracy of the volumes pipetted. Standard curves using concentration gradient increases of 1, 2, 3, 4X etc. of L-Epinephrine in 0.01N HCl provided a linear response of fluorescence to concentration. At no time were samples with partial hemol-

ysis contamination found to undergo satisfactory molecular rearrangement or the development of fluorescence.

Glucose Analysis

The plasma samples were analyzed for glucose using the procedures presented by Hill and Kessler (1961) and Robin and Saifer (1965) as modified for the Auto Analyzer.

Lactic Acid Determination

Tissue lactic acid content was determined by a modified enzymatic procedure of Hohorst (1962). The M. longissimus sample taken at death, three- and 24-hour post-mortem, and the at death liver samples were deproteinized by adding 7.25 ml of 6.0 percent perchloric acid to 1.0 gm of tissue with vigorous stirring. The samples were centrifuged at 18,000 G for ten minutes. The supernate was decanted and neutralized in an ice bath by adding 5.0 M potassium carbonate solution in the presence of methyl orange indicator. The sample solution was then centrifuged at 500 G for ten minutes. The supernate was decanted and brought to ten ml volume with glass-distilled, deionized water, and a 1.0 ml aliquot was then diluted to 10.0 ml with deionized water.

The diluted muscle and liver tissue and ten-fold deionized water diluted plasma samples were analyzed for lactic acid concentration with the use of an Auto Analyzer. The lactic acid determination was adopted from the procedures of Hochella and Weinhouse (1965), Sigma Chemical Company (1965), and Minaire (1967) and modified for the Auto Analyzer as described by Technicon Corporation (1965a, b) and Pettigrew (1969).

Mineral Analysis

Plasma samples were analyzed for sodium, potassium, and chloride with an Auto Analyzer according to the procedures published by Technicon Auto Analyzer Methodology (1965a and 1965b).

Statistical Analysis

The data was analyzed by the Least Squares Analysis of Variance method published by Harvey (1960). In addition, the swine used in this study were separated by strain, and correlations were determined for the various physiological parameters and then tested for significance at ($P < .05$) and ($P < .01$) levels (Snedecor and Cochran, 1967).

RESULTS AND DISCUSSION

Diurnal Influence on Biological Parameters

Tabular values presented in this section include the Least Squares means for diurnal effects when mean values for both strains are combined. The figures, placed in the Appendix, show the individual genotype influences from stress prone and fat strain Poland China swine.

Cortisol and epinephrine levels

Table 1 shows Least Squares means for cortisol and epinephrine levels determined on plasma from blood samples acquired at 7:30 A.M. and 4:00 P.M. during the two-day basal observation period. No major diurnal influence was obtained for cortisol and epinephrine when both stress prone and fat strain Poland China swine values were analyzed simultaneously (Table 1).

Figures 4 and 5 reveal a trend of higher plasma cortisol in morning samples and higher epinephrine levels in the afternoon when the two strains are analyzed separately. The influence of strain on the cortisol response is depicted in Figure 4 showing a significant ($P < .05$) strain difference. The diurnal effect on secretory levels of cortisol was also reported by Murphy et al. (1963), Murphy (1967a), and Steinhauf et al. (1969a). Whipp et al. (1970) measured hydrocortisone concentrations in peripheral blood of swine and observed minimal concentrations at 4:00 P.M. and maximum concentrations at 8:00 A.M. Weiss et al. (1970) reported similar results for cortisol on blood samples obtained from swine at 8:00 A.M., 4:30 P.M., and midnight.

The significant ($P < .05$) strain effect on cortisol obtained on the swine used in this study revealed stress prone swine cortisol both in the

morning and afternoon exceeded cortisol levels of the fat strain Poland China swine. Weiss et al. (1971) reported strain differences for adrenocortical secretion indicating lean strain swine possessed higher circulating levels of 17-OHCS than fat strain pigs. Known genotype of swine, therefore, is of major importance in conducting swine physiology research.

Figure 5 shows basal epinephrine values at the two sampling times. The epinephrine strain influence presented in Figure 5 shows higher values from the afternoon samples than for the samples collected in the morning. This suggests that cortisol and epinephrine levels fluctuate in opposite directions, at least under the conditions in which these pigs were maintained and rested samples collected. White et al. (1968) indicated that epinephrine mobilizes energy reserves such as fatty acids as well as initiates glucose mobilization, while adrenal glucocorticoids potentiate the storage or deposition of energy. The opposite diurnal influence on elevated cortisol and epinephrine levels (Table 1) agree with the physiological mechanism expressed by White et al. (1968).

A significantly ($P < .05$) higher basal level of plasma epinephrine was obtained for the fat strain Poland China pigs when compared to the stress prone swine (Figure 5). The significant ($P < .01$) strain effect on circulating glucose (Figure 6) would indicate greater mobilization of glucose in the stress prone swine, and, therefore, epinephrine in these stress prone individuals may be more rapidly degraded, accounting for the lower circulatory concentrations of the hormone. Selection for maximum muscle development and minimum fat deposition in swine has apparently shifted the metabolic and endocrine interrelationships of growth and biological function.

Table 1. Least squares means for plasma cortisol, epinephrine, and glucose during basal, non-stress observations

No. of observations	Time	Cortisol μg %	Epinephrine ng/ml	Glucose** mg %
72	A.M.	2.98	11.93	101.33
72	P.M.	2.82	12.10	161.94
SE		±0.23	±0.54	±15.68

**Significant ($P < .01$) diurnal influence.

Plasma glucose

A significant ($P < .01$) diurnal effect upon circulating glucose is shown in Table 1. Morning samples reflect lower levels than afternoon samples.

Figure 6 shows a significant ($P < .01$) strain effect for plasma glucose with stress prone pigs having higher levels of circulating glucose than the fat strain Poland China swine. This would indicate the energy mobilizing effect of epinephrine and the possible greater epinephrine degradation in response to greater glucose mobilization when stress prone swine are compared with fat strain Poland China pigs. The lower circulatory cortisol levels for the fat strain Poland China pigs (Figure 4), higher plasma epinephrine levels (Figure 5), and lower circulatory glucose (Figure 6) indicate less energy mobilization and greater energy deposition than in the stress prone pigs. These results would justify the increased deposition of adipose tissue in the fat strain Poland China swine (Figure 1) and is sup-

ported by the data of Weiss et al. (1971) in a comparative study of fat strain and lean strain swine.

The high standard error for diurnal plasma glucose (Table 1) accounts for the significant ($P < .01$) animal variation shown in Appendix Table 17. Also, the elevated glucose level from afternoon sampling times (Table 1) exceeds the values from the strain afternoon glucose data (Figure 6) due to one animal in each strain possessing extremely high levels of P.M. plasma glucose.

Plasma lactate and blood pH

No major diurnal influence was observed for plasma lactate and blood pH during the basal non-stress observation (Table 2). Figure 7 reveals no major strain difference in plasma lactate when samples were collected under non-stressed conditions from stress prone and fat strain swine.

Monitoring plasma lactate is important since high lactate levels lead to adrenal cortical activation (Stickney and Van Liere, 1953; Topel, 1968a). In studies of induced hemorrhagic shock, Weil and Abdelmonen (1970) showed lactate to serve as a sensitive predictor in clinical cases of shock for survival. Observation of basal non-stress lactate concentration, therefore, becomes important in experimentation designed to study stress and shock.

Table 2 does not indicate a diurnal influence on plasma pH, and this would appear logical since no major diurnal effect was shown for plasma lactate, a primary source of H^+. However, Figure 8 shows a significant ($P < .01$) strain effect with the fat strain Poland China swine possessing lower blood pH than the stress prone pigs. This response may appear unusual at first until close observation of the data is encountered. In

this study, blood pH was measured accurately to 0.001 units and thus very small deviations can be monitored critically. The actual values in Figure 8 of 7.404 for the fat strain Poland Chinas versus 7.456 for the stress prone swine from the morning collection reveal small but significant ($P < .01$) differences. These differences probably have limited, if any, physiological significance during the basal non-stress observation period studied.

Table 2. Least squares means for plasma lactate and blood pH during basal non-stress observation

No. of observations	Time	Lactate mg %	pH
72	A.M.	16.78	7.438
72	P.M.	17.55	7.435
SE		±1.57	±0.005

Plasma, sodium, potassium, and chloride levels

Least Squares means for plasma sodium, potassium, and chloride during non-stress basal observation are shown in Table 3. No major diurnal effect was observed for these three circulating electrolytes. Figures 10 and 11 indicate a significant ($P < .01$) effect of strain on plasma potassium and chloride. Figure 10 indicates that basal values from stress prone swine for plasma potassium were lower than for fat strain Poland Chinas, especially for the P.M. collection time.

The observation of electrolytes and especially potassium in the study or stress and shock has been substantiated by Lillehei et al. (1964), Sicuteri et al. (1965), Daugherty et al. (1967), Sicuteri (1967), Skinner

and Powell (1967), and Sicuteri et al. (1970). These authors attribute the greatest vasoactivity of all the major monovalent cations in the blood to potassium. Moreover, potassium is cited as a pain mediator and a local determinant eliciting skeletal muscle vasodilation during exercise by these researchers.

Table 3. Least squares means for plasma sodium, potassium, and chloride during basal non-stress observation

No. of observations	Time	Sodium meq/l	Potassium meq/l	Chloride meq/l
72	A.M.	134.18	4.28	96.94
72	P.M.	134.99	4.33	96.33
SE		±1.14	±0.05	±0.59

The significant ($P < .01$) strain difference for plasma glucose and potassium and significant ($P < .05$) strain influence upon circulating cortisol and epinephrine levels further substantiates statements of Weiss et al. (1970) and Weiss et al. (1971) that the influence of genotype on physiological parameters is of major importance and cannot be overlooked in the study of biological science. Steinhauf et al. (1969b) reported that there were considerable fluctuations in the level of examined cortisol, glucose, and lactate between the animals as well as between the different times of investigation. The significant interactions and standard error magnitudes presented in the data obtained from this study further substantiate the work of Steinhauf et al. (1969b).

Influence of Adrenergic Blocking Agents

Antemortem observations

The stress prone swine used in this study, which received phenoxybenzamine, all suffered from exhaustion after being subjected to physical stress. One of the six α block treated stress prone pigs withstood five minutes of physical stress, two individuals collapsed after four minutes, and one individual collapsed after three minutes, two and one-half minutes, and one and one-half minutes of stress, respectively. The physical exhaustion was characterized by irregular deep and forceful respiration, tail and ear tremors, blotching of the lateral and ventral skin areas, abnormal vocalization, and inability to remain stationary upon the individual's feet. These conditions were observed to a minor degree in the stress prone control swine, while only increased respiration rate was observed in the fat strain Poland China controls administered the β block and then stressed five minutes.

Topel et al. (1968a) and Weiss et al. (1970) reported cutaneous blotching, impairment of respiration, muscular tremors, and traumatic collapse in describing the characteristics of the porcine stress syndrome.

The peripheral blood pooling effect of phenoxybenzamine was reported by Block et al. (1966). These authors found α receptors present to the greatest extent in visceral and cutaneous smooth muscle. Lewis and Mellander (1962) reported that along with producing arteriolar relaxation, phenoxybenzamine induced loss of venular tone, thus reducing capillary hydrostatic pressure and enlarging the venular capacitance. Prolonged reduction of blood to vital areas leads to lethal changes including meta

bolic acidosis as well as stagnation and pooling of blood (Block et al., 1966; Perlroth and Harrison, 1969; Armstrong, 1970).

The physical collapse and traumatic-like response of the phenoxybenzamine treated stress prone swine used in this study responded similarly to rats studied by Eckenhoff and Cooperman (1965). These researchers found that pretreatment with phenoxybenzamine one to five hours in advance of shock reduced the incidence of shock death but made rats more susceptible to acute traumatic death.

The phenoxybenzamine treated fat strain Poland China swine exhibited minimal signs of physiological discomfort in response to five minutes of physical stress. These individuals displayed an increased but regular respiration rate but none of the trauma-like responses shown by the stress prone swine after α block treatment and stress.

None of the β block (Inderal) treated stress prone swine collapsed due to administration of physical stress for a duration of five minutes. These individuals revealed indications of fatigue similar to those of an athlete or laborer after strenuous physical work but by no means presented indication of collapse. Respiration was deep but not irregular nor necessarily rapid. Cutaneous blotching was observed only to a minimal degree. The fat strain Poland China swine administered Inderal and then stressed for five minutes withstood the physical exercise with no apparent impairment physiologically other than an observed increase in respiration rate.

These physical observations agree with work by Block et al. (1966) when he reported that propranolol produced a decrease in externally measured indicies of myocardial mechanical effort and, consequently, a fall in myocardial oxygen demand. Copeland (1967) reported that Inderal pro-

duced a fall in heart rate, a decrease in cardiac output, a decrease in resting stroke volume, a decrease in ventricular diastolic and systolic volume, and, therefore, a change in tension of the myocardial wall with oxygen consumption falling by 25 percent. Ulrych et al. (1968) and Wolfson and Gorlin (1969) also found β blockade reduced cardiac output and peripheral vasodilation. The less drastic observed physiological changes noted in the β block treated stress prone and fat strain Poland China pigs in comparison to the α block treated pigs can be explained by the findings of these authors.

Another subjective observation on the swine used in this study revealed the stress prone individuals to exhibit hypertensive characteristics, especially when compared with the activity of the fat strain Poland China pigs. Hypertension has long been ascribed to increased peripheral resistance (Page and McCubbin, 1956), therefore, its treatment has been primarily directed toward blood pressure reduction by decreasing vascular resistance. The β block treated pigs, especially the stress prone individuals used in this study, exhibited less subjective indication of hypertension than did the control or α block treated stress prone swine.

Cortisol relationships

Data presented in Table 4 are Least Squares means for plasma cortisol and epinephrine obtained after administration of adrenergic blocking agents and a five-minute period of physical stress.

No major strain difference was observed for cortisol levels after stress in this portion of the study due primarily to the magnitude of variation between animals within and between strains. The high cortisol stan-

Table 4. Least squares means for plasma cortisol and epinephrine after pre-stress adrenergic blockade administration and five-minute physical stress

Group	Cortisol μg %	Epinephrine* ng/ml
Stress prone controls	7.15	5.60
Stress prone α block	7.52	7.30
Stress prone β block	6.12	7.66
Fat strain P.C. controls	5.16	11.24
Fat strain P.C. α block	7.98	8.17
Fat strain P.C. β block	7.13	8.73
SE	±1.39	±1.17

*Significant ($P < .05$) strain influence.

dard error (Table 4) reflects substantial animal variation which corresponds to the data presented by Weiss et al. (1970).

Observation of Figure 4 reveals the significant ($P < .01$) effect of stress on cortisol elevation for all three treatments, control, α and β blockade. Significantly ($P < .01$) higher levels of circulating cortisol occurred in all three treatments when stressed values were compared with non-stress basal cortisol levels in both strains. This observed increased adrenal cortical activity agrees in part with data from individual swine reported by Judge et al. (1968), Topel (1968b), Marple et al. (1969), and Weiss et al. (1970). These researchers also reported a variation in adrenocortical response to stress since some individual pigs secreted their maximum but lower cortical steroid levels when stress was induced. Genotype of the swine studied appeared to influence the level of cortical activity, high, intermediate, or low, for the individual swine studied. The animal variation revealed in this study agrees with these reports.

Epinephrine relationships

A significant ($P < .05$) influence of strain upon plasma epinephrine levels after stress for all treatments is shown in Table 4. The fat strain Poland China swine possessed higher circulatory levels than did the stress prone swine. These results agree with Yamori et al. (1970) who found norepinephrine concentration in lower brainstem and hypothalmus of genetically hypertensive rats significantly lower than in control rats. These authors suggested that catecholamine mechanisms in the central nervous system may play an important role in the regulation of blood pressure and genetic hypertension. von Euler (1964) reaffirmed earlier proposals that emotional stresses which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion.

The significant ($P < .05$) influence of strain on epinephrine levels in response to stress follows the findings of a significant ($P < .05$) strain influence on diurnal epinephrine levels indicated earlier for the swine used in this study. Results shown in Figure 5 show significant ($P < .01$) declines in circulating epinephrine when stressed versus non-stressed levels are compared for each strain within each treatment group. The stressed samples obtained in this study were acquired after a five-minute stress period or the physical collapse of the individual pig, whichever came first. Such collection procedure may allow sufficient time for the initial secretory burst of epinephrine, in response to induced stress, to be degraded. Jones and Blake (1958) reported the rate of epinephrine removal from the circulation to be very rapid.

Observation of Figures 6 and 7 show marked elevation of plasma glucose and lactate for all treatments in response to stress. This would indicate major energy mobilization induced by epinephrine potentiation (Crowell and Guyton, 1962). The reduced epinephrine levels observed in response to stress, in the presence of elevated plasma glucose and lactate, indicate major amounts of epinephrine are probably removed rapidly from the circulatory system. The physiological interrelationship of cortisol and epinephrine levels during stress conditions is further supported in this study. During stress, cortisol levels increased (Figure 4), and epinephrine levels decreased (Figure 5). This supports the work of Ramey et al. (1951) when he reported that adrenocortical hormones were essential to provide a "permissive" action for the pressor effect of catecholamines. According to Ramey and Goldstein (1957), in the absence of adrenal cortical steroids, the threshold for epinephrine and norepinephrine action is greatly raised. The data from swine used for this dissertation would indicate adrenocortical potentiation of adrenal medullary hormones occurs in response to induced physical stress.

Epinephrine acts to induce the cutaneous blotching observed in the stress prone swine used in this study. Ramey et al. (1951) reported that under stressed conditions, epinephrine release produces a shift of blood flow from the splanchnic area to the working muscle and periphery. Dietzman et al. (1967) reported that the sympathoadrenal stress response is greatest in the vasoactive, adrenergically sensitive viscera and skin; these results would indicate in part the physiological justification for the cutaneous lateral and ventral blotching observed in the stress prone swine used in this study.

Shanks (1967) reported that propranolol blocked the vasodilation produced by adrenaline and potentiated the epinephrine vasoconstriction effect. The effect of propranolol on reduction of adverse physiological response to stress associated with epinephrine induced energy metabolism on swine used in this study has been previously indicated. Research by Block et al. (1966), Copeland (1967), Ulrych et al. (1968), and Wolfson and Gorlin (1969) substantiates these observations.

Glucose relationships

Least Squares means for plasma glucose and lactate and blood pH after pre-stress adrenergic blockade followed by five minutes of physical stress are shown in Table 5.

Table 5. Least squares means for plasma glucose and lactate and blood pH after pre-stress adrenergic blockade and five-minute physical stress

Group	Glucose mg %**	Lactate mg %**	pH**
Stress prone controls	157.83	170.50	7.184
Stress prone α block	164.90	263.00	7.055
Stress prone β block	159.18	205.17	7.179
Fat strain P.C. controls	105.50	60.98	7.321
Fat strain P.C. α block	126.10	54.50	7.390
Fat strain P.C. β block	106.43	46.50	7.375
SE	$\pm$10.01	$\pm$18.38	$\pm$0.040

**Significant ($P < .01$) strain influence.

A significant ($P < .01$) strain effect on circulating plasma glucose was obtained from samples collected after adrenergic blockade and induced stress. The stress prone swine had the highest levels of plasma glucose. This agrees with the significantly ($P < .05$) lower circulating epinephrine levels for the stress prone swine in response to induced physical stress. These individuals apparently utilize their epinephrine secretion very rapidly to enhance the glucose mobilization seen in Table 5 and Figure 6. In addition, the elevated cortisol levels in response to stress (Figure 4) potentiate this physiological reaction.

Figure 6 reveals a significant ($P < .01$) elevation of circulating glucose for both strains and each treatment when after-stress samples were compared with basal pre-stress plasma glucose concentrations. This agrees with the work of Crowell and Guyton (1962). White et al. (1968) also stated that glucose acts as the initial substrate for major energy metabolic pathways leading to energy rich compound synthesis. Exercise or stress increases energy utilization and glucose mobilization as a result of epinephrine induced potentiation. This justifies the elevated glucose levels and reduced epinephrine levels observed in this study in response to stress.

Table 5 shows α block treated pigs in both strains possessed higher levels of circulating glucose than the respective within-strain control and β block treated swine in response to physical stress. The suggested reduced rate of blood flow as a result of Inderal infusion, as well as less readily apparent expression of excitement, hypertension, or exhaustion in β block treated pigs, would suggest a lower level of energy mobilization. The excited, hypertensive, fatigued α block treated pigs would be expected

to have higher circulatory glucose as the pigs respond to visceral and cutaneous vasoconstriction and attempt to synthesize high energy compounds to replace those utilized in response to the induced stress.

Lactate relationships

A significant ($P < .01$) strain effect on plasma lactate was obtained in this study (Table 5). The stress prone swine possessed significantly greater amounts of circulatory lactate for all three treatments than the fat strain Poland China pigs under similar conditions. These results agree with the significant ($P < .01$) effect of strain on plasma glucose since lactate is one of the primary metabolites of glucose (White et al., 1968). Figure 7 reveals a significant stress effect upon circulating lactate for both stress prone ($P < .01$) and fat strain Poland China swine ($P < .05$). All three treatments showed significant ($P < .01$) plasma lactate elevation after stress when compared to basal pre-stress levels.

Glenn et al. (1961) and White et al. (1968) reported that adrenal glucocorticoids, especially hydrocortisone, influence the conversion of lactate to glycogen. Figure 4 shows evidence of such biochemical activity since fat strain Poland China swine in both the α and β block treatment groups secreted higher levels of cortisol in response to stress than did the respective stress prone α and β blockade pigs. It would appear that genetic selection for muscling in swine has altered adrenal cortical response to stress and thus implies the importance of known genotype in swine physiology research. Table 5 and Figure 7 both show significantly lower ($P < .01$) levels of plasma lactate in response to stress for the fat strain Poland China pigs than for the stress prone swine.

Figure 4 depicts significant ($P < .01$) adrenal cortical activity in response to induced stress. However, the α block treated stress prone swine show less cortisol elevation upon induced stress than the stress prone control or stress prone β block pigs. Figure 7 reveals the α block stress prone swine to have the greatest elevation in plasma lactate in response to stress. These data agree with the concepts of Stickney and Van Liere (1953) and Topel (1968a) in reports that anoxia and high blood lactate lead to adrenal cortical activation. According to Thorn et al. (1945), under these circumstances, an increase in adrenal steroids is necessary for circulatory homeostasis and to maintain life.

The high plasma lactate values of the α block stress prone swine would suggest the existance of an anoxic condition. Huckabee (1958a), Broder and Weil (1964), and Peretz et al. (1965) reported that lactate is a satisfactory indirect measurement of oxygen consumption or deficit. Confirmation of such a condition appeared realistic upon subjective observation of the α block stress prone individuals, five of which collapsed from the induced stress and all six exhibiting deep, irregular forced respiration. The rapid, deep but rhythmic breathing of the control and β block stress prone swine indicate a similar but less severe condition, and Figure 7, presenting plasma lactate values, would suggest this. The exhibition of only minor respiration increase in the fat strain Poland China swine and thus a decided less anoxic condition is confirmed by the significantly ($P < .01$) lower stress elevations of plasma lactate for the control, α and β block treatments shown in Figure 7. The summary statement of Crowell and Smith (1964) and Weil and Abdelmonen (1970) seems applicable:

the reduction of oxygen consumption during shock as well as the increase in blood lactate are related to physiological damage and survival.

Huckabee (1958b) and Schumer (1968) stated that circulatory anoxia accounts for the accumulation of lactate and, in part, for the progressive acidosis characteristics of shock. Schumer and Sperling (1968) stated metabolic acidemia produces lysosome membrane disruption with the outpouring of the lytic enzymes causing death of the cell. According to Wilkens et al. (1970), the ability of the microvascular system to respond to the ever changing metabolic needs of the various tissues is a fundamental requirement for maintaining homeostasis.

pH relationships

Table 5 shows a significant ($P < .01$) effect of strain on blood pH with the stress prone swine of all treatments responding to a five-minute duration of physical stress with a lower blood pH than the respective fat strain pigs. Figure 8 shows no major difference in stressed blood pH versus basal pH for the fat strain Poland China swine. Such data would indicate little if any incidence of acidosis occurring in these pigs, which is further substantiated by plasma lactate values given in Table 5 and Figure 7.

However, the stress prone pigs show a definite acidosis condition with the low pH values presented in Table 5 and a significant ($P < .01$) drop in stressed versus basal pre-stress pH values shown in Figure 8. The α block stress prone pigs (Figure 8) show a much greater pH drop due to stress than the stress prone control or β block pigs. These data agree with the lactate and cortisol discussion previously presented and further elucidate the

physiological reason for the catastrophic, traumatic responses observed in the α block stress prone swine when subjected to physical stress: circulatory acidosis.

Vasodilation following a decrease in blood pH has been demonstrated early in scientific investigation and confirmed by many (Krogh, 1929; Fleisch et al., 1932; Kester et al., 1952; Zsoter et al., 1961; Molnar et al., 1962. Lillehei et al. (1964) observed there is always a lowering of blood pH as shock progresses. Marple (1968) reported that a very high content of lactic acid develops in the plasma and muscle after exercise resulting in death for extreme individuals. Death from acute anoxia or acidosis reveals that the fall in blood pressure may be due to the diminished constrictor action of various hormones, the absence of adequate oxygen, or a low blood pH. Also, epinephrine and norepinephrine probably lack their normal pressor effect (Shurtshin et al., 1948; Van Loos et al., 1948; Nahas and Payart, 1967). Observation of the α block stress prone pigs in this study reflect the consensus of these authors. The stress prone α block pigs possessed low epinephrine levels after stress, extremely high plasma lactate, an indirect indicator of inadequate oxygen supply, and very low blood pH in response to induced physical stress.

Sodium, potassium, and chloride

Least Squares means for plasma sodium, potassium, and chloride after pre-stress adrenergic blockade and five minutes of physical stress are shown in Table 6.

Table 6 reveals a significant ($P < .05$) influence of strain on plasma sodium with the stress prone swine possessing the higher levels. No major

Table 6. Least squares means for plasma sodium, potassium, and chloride after pre-stress adrenergic blockade and five-minute physical stress

Group	Sodium meq/l*	Potassium meq/l**	Chloride meq/l
Stress prone controls	134.83	4.57	98.38
Stress prone α block	141.92	5.41	102.93
Stress prone β block	138.87	5.32	98.52
Fat strain P.C. controls	135.45	3.92	107.42
Fat strain P.C. α block	126.18	3.16	96.10
Fat strain P.C. β block	130.20	4.20	90.80
SE	$\pm$4.06	$\pm$0.32	$\pm$4.49

*Significant ($P < .05$) strain influence.

**Significant ($P < .01$) strain influence.

strain or treatment differences for plasma chloride were determined (Table 6). The variability in directionality of the graphs in Figures 9 and 11, especially for the α block stress prone and fat strain Poland China swine, exemplify the significant animal variation observed within treatment group and strain in this study. Strain effects on plasma ion concentration were also reported by Weiss et al. (1971), and stress influence was indicated by Weiss et al. (1970). Many of the ionic shifts are not fully understood, which is the case for sodium and chloride observed in this study.

Plasma potassium data is also presented in Table 6. A significant ($P < .01$) strain influence was observed. Similar results were reported by Weiss et al. (1971). Table 6 and Figure 10 show the stress prone swine to possess higher levels of plasma potassium than the fat strain Poland China swine after stress. The major response to treatment was observed in the α block group with a substantial increase of plasma potassium after stress

for the stress prone swine and a similar decrease for the γ block fat strain Poland China pigs. A substantial increase in plasma potassium concentration was also observed from β blocked stress prone swine when stressed versus non-stressed levels were compared (Figure 10).

Lillehei et al. (1964) stated that there are marked shifts in electrolytes during hemorrhagic shock. Serum potassium elevations were the most striking. Skinner and Powell (1967) reported that potassium as well as other metabolites acts as a local determinant eliciting skeletal muscle vasodilation during exercise. Daugherty et al. (1967) reported potassium to possess the greatest vasoactivity of the major monovalent cations in blood. The previously described relationships for plasma cortisol, epinephrine, glucose, lactate, and blood pH with respect to the adrenergic blockade and physical stress administration are confirmed by these authors' findings in view of the plasma potassium data obtained in this study.

M. longissimus Characteristics

Table 7 presents Least Squares means for M. longissimus lactate, pH, and color zero, three, and 24 hours post-mortem.

A significant ($P < .01$) strain influence on M. longissimus lactate was obtained. The stress prone swine possessed higher levels of muscle lactate at each observation time and in each treatment group when compared to the fat strain Poland China pigs (Table 7 and Figure 12). These data are consistent with the physiological and biochemical results discussed previously when stress prone swine were observed to have higher levels of plasma glucose, lactate and potassium, and lower blood pH than the fat strain pigs. Kastenschmidt and Briskey (1966) concluded that higher levels of lactate in

Table 7. Least squares means for M. longissimus lactate, pH, and color 0, 3, and 24 hours post-mortem

	Lactate mg % **[a]	pH**	Color**
Stress prone 0 hr.			
Control	3.3	6.37	13.8
α block	3.4	6.28	13.0
β block	3.2	6.37	12.5
Stress prone 3 hr.			
Control	5.9	5.96	15.5
α block	5.4	5.99	16.2
β block	5.5	5.90	14.4
Stress prone 24 hr.			
Control	7.4	5.47	21.3
α block	7.0	5.52	20.7
β block	7.6	5.46	22.0
Fat strain P.C. 0 hr.			
Control	2.8	6.64	13.2
α block	3.4	6.54	12.7
β block	2.7	6.74	14.2
Fat strain P.C. 3 hr.			
Control	3.9	6.24	13.1
α block	4.6	5.94	16.2
β block	3.7	6.39	14.5
Fat strain P.C. 24 hr.			
Control	6.6	5.47	21.1
α block	6.3	5.40	20.8
β block	6.4	5.64	19.6

[a]Significant ($P < .01$) strain influence.

**Significant ($P < .01$) time influence.

in muscle result from a rapid rate of post-mortem glycolysis and is associated with an oxygen debt prior to death.

Bate-Smith (1948), Lawrie (1958), Briskey (1959), Wismer-Pedersen (1959), Briskey et al. (1960), and Judge et al. (1968) determined dark, firm muscle was higher in pH and lower in free water than pale, soft muscle. Briskey and Wismer-Pedersen (1961) and Sayre et al. (1964) determined that a rapid significant decrease of muscle pH to 5.1 one and one-half hours post-mortem yielded pale, soft and exudative pork.

M. longissimus lactate, pH, and color (Table 7) values show a significant ($P < .01$) time influence. The lactate and pH values complement each other since pH is a measure of H^+ concentration, primarily supplied by lactate. No major strain differences were observed for color and pH. The general increase in M. longissimus lactate content and reciprocal pH decline with advance in time post-mortem conform to earlier research (Lawrie, 1958; Briskey, 1959; Wismer-Pedersen, 1959; Briskey et al., 1960; Judge et al., 1968; Weiss et al., 1970; Weiss et al., 1971).

Table 7 reflects no major strain influence on muscle color for the swine used in this study. However, a significant ($P < .01$) time effect was determined with a lightening effect occurring with advance in time post-mortem. These data agree with those of Weiss et al. (1970) and Weiss et al. (1971). However, Weiss et al. (1971) in a comparison of lean and fat strain pigs found a significant strain influence on muscle color with lean strain pigs possessing lighter muscle color than fat strain pigs. Adrenergic blockade in this study may have influenced muscle color in contrast to non-exogenous material administration in the study reported by Weiss et al. (1971).

The data presented in this dissertation reveal that normal, acceptable muscle quality based on color, pH, and lactate evaluation can be produced from genetically based stress prone swine as well as from genetically selected fat strain pigs. However, within the ham musculature of the stress prone swine used in this study, frequent occurrence of microcirculatory hemorrhage was observed in the form of "blood spots". The adverse implications for processing and economic losses as well as physiological significance of this observation may be of major importance (Figure 3).

Liver Lactate Levels

Table 8 and Figure 15 reveal a significant ($P < .05$) effect of strain on ten-minute post-mortem liver lactate concentration. The stress prone swine possessed higher levels of liver lactate for all treatments when compared with the fat strain Poland China pigs. This analysis was conducted since the liver is a primary site of lactate conversion to glycogen (White et al., 1968). The data substantiate the plasma and M. longissimus lactate data previously presented and discussed.

Table 8. Least squares means for ten-minute post-mortem liver

Strain*	Control mg %	∝ block mg %	β block mg %
Stress prone	1.4	1.3	1.3
Fat strain P.C.	1.1	0.9	1.1

*Significant ($P < .05$) strain influence.

ASSOCIATION OF PHYSIOLOGICAL PARAMETERS

Correlation Coefficients between Basal Values

Epinephrine

Table 9 presents correlation coefficients between stress prone and fat strain Poland China swine for basal plasma epinephrine and basal plasma cortisol, glucose, lactate, potassium, and blood pH.

Table 9. Correlation coefficients between plasma epinephrine and basal plasma cortisol, glucose, lactate, potassium, and blood pH

		Stress prone	Fat strain P.C.
Epinephrine A.M. vs.	cortisol A.M.	-0.028	-0.396
	glucose A.M.	0.105	-0.066
	lactate A.M.	-0.306	-0.070
	blood pH A.M.	0.000	0.351
	potassium A.M.	-0.455	0.207
Epinephrine P.M. vs.	cortisol P.M.	-0.413	-0.597**
	glucose P.M.	0.132	0.342
	lactate P.M.	-0.413	-0.334
	blood pH P.M.	0.119	-0.490*
	potassium P.M.	-0.453	0.160

*Significant ($P < .05$).

**Significant ($P < .01$).

The decidedly lower cortisol and higher epinephrine levels from P.M. samples for both strains (Figures 4 and 5) account for the negative epinephrine versus cortisol correlations of -0.413 for the stress prone strain and significant ($P < .01$) -0.597 correlation for the fat strain Poland China swine. The correlation coefficients for basal epinephrine versus basal lactate and glucose reveal no major differences.

The significant ($P < .05$) negative correlation (-0.490) between epinephrine and blood pH values from samples collected in late afternoon for the fat strain Poland China pigs appears to be associated with the negative epinephrine versus lactate correlation (-0.334) obtained on samples collected during the same time period for the fat strain of swine. The significant negative correlation (-0.597) for epinephrine versus cortisol values from afternoon samples may indicate an inverse function for these substances on blood pH and thus the lactate is not converted to glycogen as rapidly when cortisol levels are lower. It is also possible that within the fat strain Poland China swine, the buffer system may not react rapidly under non-stress conditions to counteract the rise in H^+.

Basal plasma epinephrine versus plasma potassium for the stress prone swine approached significance (-0.455 morning collection and -0.453 afternoon collection). These relationships reflect results in earlier research (Lillehei et al. (1964) and Block et al. (1966)) that revealed potassium variability in hypertensive individuals as well as potassium concentration change in response to stress. The data reported in this dissertation would further substantiate the importance of genotype and selection pressure on altering physiological function and biological mechanisms. The importance of potassium in nerve and muscle membrane potantials indicates critical consideration is needed in the evaluation of neuromuscular and physiological function.

Cortisol

Correlation coefficients between stress prone and fat strain Poland China swine for basal plasma cortisol versus basal plasma glucose, lactate, potassium, and blood pH are shown in Table 10.

Table 10. Correlation coefficients between basal plasma cortisol and basal plasma glucose, lactate, potassium, and blood pH

		Stress prone	Fat strain P.C.
Cortisol A.M. vs.	glucose A.M.	0.190	0.237
	lactate A.M.	0.000	0.026
	pH A.M.	0.136	0.230
	potassium A.M.	0.014	-0.310
Cortisol P.M. vs.	glucose P.M.	-0.160	-0.314
	lactate P.M.	0.076	-0.127
	pH P.M.	0.001	0.494*
	potassium P.M.	0.084	-0.234

*Significant ($P < .05$).

The diurnal cortisol influence Figure 4 is revealed in the correlation coefficients presented in Table 10. Figure 4 shows both strains of swine to have lower cortisol levels at the afternoon collection time, while Figure 6 shows no major diurnal effect on plasma glucose. These data result in the negative afternoon cortisol versus glucose correlations in Table 10. The cortisol versus lactate correlations (Table 10) reveal no major relationships in this study.

The significant correlation ($P < .05$) for fat strain Poland China pigs between afternoon cortisol versus blood pH values can be associated with the fat strain correlation of (0.127) for afternoon cortisol versus lac-

tate. As plasma cortisol declines, lactate increases causing a fall in blood pH, and a positive cortisol-blood pH relationship is established.

The negative correlations for cortisol versus plasma potassium for the fat strain Poland China swine during both morning and afternoon sample collection and the low but positive values for the stress prone line again suggest the importance of known genotype in physiology research. These data also reflect the diurnal cortisol and potassium shifts shown in Figures 4 and 10.

Blood pH

Within strain correlation coefficients are shown in Table 11 for basal blood pH and basal glucose, lactate, and potassium.

Table 11. Correlation coefficients between basal blood pH and basal plasma glucose, lactate, and potassium

	Stress prone	Fat strain P.C.
pH A.M. vs. glucose A.M.	0.094	0.419
lactate A.M.	-0.573*	0.335
potassium A.M.	-0.249	-0.612**
pH P.M. vs. glucose P.M.	-0.187	-0.280
lactate P.M.	-0.020	0.347
potassium P.M.	-0.153	0.095

*Significant ($P < .05$).

**Significant ($P < .01$).

The negative correlations for blood pH versus plasma lactate at both sample collection times for the stress prone swine reveal a decline in pH as lactate increases which suggests plasma lactate changes are of sufficient magnitude in relation to pH to denote the variation. A positive relationship for the fat strain Poland China swine for the same parameters and time periods was obtained.

The opposite signs for correlations between strains in blood pH and plasma glucose concentration (Table 11) for both collection times indicates the importance of genotype and diurnal effects on monitoring physiological changes in swine. The genotype and diurnal influence is further exemplified in Table 11 when blood pH and plasma potassium are correlated. Fat strain Poland China swine showed a significant ($P < .01$) negative correlation (-0.612) between morning blood pH and plasma potassium but a low, positive correlation (0.095) for the afternoon relationship. Both morning and afternoon correlations of blood pH and plasma potassium for stress prone swine were negative and of low magnitude.

Correlation Coefficients between Basal Values and Post-Stress Parameters

Epinephrine

Table 12 presents within strain correlation coefficients for basal morning and post-stress epinephrine levels and post-stress cortisol, glucose, lactate, pH, potassium, and epinephrine values.

The epinephrine versus cortisol correlations in Table 12 reflect a low relationship between the diurnal elevation of epinephrine secretion within strain and cortisol decline when samples are collected in the morning and afternoon (Figures 4 and 5). Figure 5 also shows epinephrine levels to

Table 12. Correlation coefficients between basal morning and post-stress plasma epinephrine and post-stress cortisol, glucose, lactate, pH, potassium, and epinephrine

		Stress prone	Fat strain P.C.
Epinephrine A.M. vs.	post-stress cortisol	-0.244	0.109
	post-stress glucose	0.049	0.175
	post-stress lactate	0.158	-0.338
	post-stress pH	-0.193	0.378
	post-stress potassium	-0.100	-0.576*
	post-stress epinephrine	0.020	-0.162
Epinephrine post-stress vs.	post-stress cortisol	-0.239	-0.026
	post-stress glucose	-0.203	-0.243
	post-stress lactate	0.181	0.262
	post-stress pH	-0.256	0.023
	post-stress potassium	0.218	0.167

*Significant ($P < .05$).

decline after physical stress which substantiates the negative correlation coefficients (Table 12) for post-stress epinephrine versus post-stress cortisol since cortisol levels increased in response to stress (Figure 4).

Epinephrine is known to mobilize glucose and thus positive and possibly significant relationships between post-stress epinephrine levels and plasma glucose levels after stress may have been expected. Figure 5 shows epinephrine levels were lower after stress, and Figure 6 shows glucose levels increased in response to stress, therefore, negative correlations as seen in Table 12 are realistic. This relationship and the data presented in Figures 5 and 6 would indicate epinephrine secretion, in response to induced stress, did potentiate glucose mobilization, however, due to the rapid degradation of epinephrine and the collection procedure following

stress, the levels of epinephrine determined were actually lower than basal levels.

Figures 5 and 10 show fat strain Poland China plasma potassium concentration to decrease in the control and ◁ block pigs as the result of induced stress and morning epinephrine levels to remain high thus resulting in the significant ($P < .05$) correlation shown in Table 12. Strain as well as treatment appear to influence this correlation.

Cortisol

Within strain correlation coefficients for morning and post-stress cortisol and post-stress epinephrine, glucose, lactate, potassium, cortisol, and blood pH are shown in Table 13.

No major relationship between cortisol and post-stress plasma epinephrine, glucose, lactate, blood pH, and potassium level is shown in Table 13.

Table 13. Correlation coefficients between morning and post-stress cortisol and post-stress epinephrine, glucose, lactate, potassium, cortisol, and blood pH

		Stress prone	Fat strain P.C.
Cortisol A.M. vs.	post-stress epinephrine	-0.196	0.139
	post-stress glucose	-0.386	-0.308
	post-stress lactate	0.115	-0.193
	post-stress pH	-0.230	-0.103
	post-stress potassium	0.165	0.371
	post-stress cortisol	0.744**	0.109
Cortisol post-stress vs.	post-stress glucose	0.077	0.311
	post-stress lactate	-0.097	-0.192
	post-stress pH	0.124	0.150
	post-stress potassium	0.139	0.143

**Significant ($P < .01$).

It might be expected that since high lactate and, therefore, low pH potentiate cortisol secretion major importance may have been observed for these relationships. The individual pig variability observed throughout the data presented in this study is reflected by no major within strain importance for these parameters.

Potassium is also a stimulant for cortisol secretion, and the positive post-stress plasma potassium versus morning and post-stress cortisol correlations (Table 13) reflect this physiological influence of potassium.

The significant ($P < .01$) positive correlation (0.744) for stress prone swine morning cortisol levels versus post-stress cortisol levels is a reflection of the treatment-stress response shown in Figure 4. The animal variation, especially in adrenocorticoid release, has been frequently presented in this dissertation. Apparently not all pigs have the same secretion potential of adrenal cortical hormones, as is further exemplified by the positive but low correlation (0.109) in Table 13 for the fat strain Poland China basal morning cortisol level versus the post-stress cortisol concentration. Individual pigs which secreted less during basal sample collection secreted less cortisol upon induced stress. This observation was reported earlier by Topel (1968a) and Weiss et al. (1970).

Glucose

Table 14 reveals within strain correlation coefficients for morning and post-stress glucose and cortisol, epinephrine, lactate, potassium, and pH values.

The non-significant correlations for basal glucose versus post-stress cortisol are shown in Table 14. These values suggest that cortisol levels

Table 14. Correlation coefficients between morning and post-stress glucose and post-stress cortisol, epinephrine, lactate, potassium, and pH

		Stress prone	Fat strain P.C.
Glucose A.M. vs.	post-stress cortisol	0.316	0.051
	post-stress epinephrine	0.205	-0.376
	post-stress lactate	0.169	-0.276
	post-stress pH	-0.144	0.083
	post-stress potassium	0.087	0.445
Glucose post-stress vs.	post-stress lactate	0.689**	0.432
	post-stress pH	-0.704**	-0.475*
	post-stress potassium	0.676**	-0.601**

*Significant ($P < .05$).

**Significant ($P < .01$).

are not highly associated with specific glucose levels in the blood, but positive relationships exist. Non-stress cortisol levels in stress prone swine are more highly related to cortisol levels after stress than the fat strain pigs. This may be associated with the higher levels of both cortisol and glucose in the blood of stress prone pigs.

Table 14 shows post-stress lactate values and basal glucose values to have a positive correlation for the stress prone pigs and, as a result, a negative correlation between basal glucose and post-stress blood pH. The lower basal glucose and the significantly lower ($P < .01$) rise in plasma lactate in response to stress resulted in a higher blood pH for the fat strain Poland China pigs and explains the respective fat strain swine correlations presented in Table 14 for blood glucose, lactate, and pH.

Increased plasma glucose in response to induced stress would result in increased plasma lactate and lower blood pH as shown in Figures 6, 7, and 8. Thus, the significant correlations for glucose levels after stress with post-stress lactate and pH (Table 14) are expected. The magnitude of the stress prone swine response to stress (Figures 7 and 8) justifies the significant effects presented in Table 14.

The significant ($P < .01$) correlations for glucose after stress and post-stress potassium indicate that the stress prone swine possess high circulating potassium in response to stress. This is shown in Figure 10 and would indicate a physiological abnormality since higher potassium levels are normally found within the cell and lower levels outside the cell. Some form of membrane or tissue change apparently occurred within the stress prone swine used in this study when subjected to stress. In contrast, a significant ($P < .01$) negative correlation between after stress glucose and post-stress potassium values for the fat strain swine was obtained.

Within strain correlation coefficients for basal morning and post-stress lactate and cortisol, epinephrine, glucose, pH, and potassium are shown in Table 15.

No major relationship is shown within strain (Table 15) for basal, morning lactate values when correlated with cortisol or glucose levels from samples collected after stress.

The positive correlation for the stress prone swine for basal morning lactate values versus post-stress potassium levels and the positive, significant ($P < .01$) relationship (0.628) between lactate and potassium (post-stress values) conform to the discussion presented on glucose and potassium relationships. The stress prone swine appear to undergo an abnormal tissue

Table 15. Correlation coefficients between morning and post-stress lactate and post-stress cortisol, epinephrine, glucose, pH, and potassium

		Stress prone	Fat strain P.C.
Lactate A.M. vs.	post-stress cortisol	0.087	0.146
	post-stress epinephrine	-0.310	-0.171
	post-stress glucose	-0.014	-0.008
	post-stress pH	-0.261	-0.321
	post-stress potassium	0.258	-0.019
Lactate post-stress vs.	post-stress pH	-0.766**	0.072
	post-stress potassium	0.628**	-0.002

**Significant ($P < .01$).

degradation in response to induced stress resulting in a potassium increase in the circulatory system. Since glucose and lactate also increase with induced stress, the respective correlations are positive. The fat strain Poland China swine do not seem to undergo a similar physiological relationship between post-stress potassium and glucose and lactate post-stress (Tables 14 and 15).

A significant ($P < .01$) negative correlation (-0.766) for the stress prone swine (Table 15) was determined between lactate values obtained after stress and post-stress blood pH levels. Less dramatic plasma lactate and blood pH changes were observed for the fat strain Poland China swine, and no significant correlations between plasma lactate and blood pH were determined.

CONCLUSIONS

1. Genetic and diurnal influences are important considerations as well as animal variation in establishing and comparing biological parameters and exogenous treatment effects.
2. Diurnal plasma parameters revealed glucose levels were significantly higher ($P < .01$) in the afternoon for simaltaneous strain analysis. Stress prone swine glucose values were significantly higher ($P < .01$) in the afternoon in contrast to no major elevation for the fat strain swine. No diurnal variation was obtained for plasma cortisol, epinephrine, potassium, chloride, lactate, or blood pH. The fat strain swine possessed significantly higher ($P < .01$) plasma potassium for both A.M. and P.M. sample collections. The fat strain swine also exhibited a significantly higher ($P < .05$) epinephrine level for morning and afternoon collection and a significantly lower ($P < .05$) cortisol level for the same collection period. The stress prone swine possessed higher chloride levels than the fat strain for both A.M. and P.M. samples.
3. Five minutes of induced physical stress increased plasma cortisol in both strains (significant $P < .01$) and resulted in a significant ($P < .01$) reduction in plasma epinephrine. Plasma glucose in response to induced stress increased significantly ($P < .01$); plasma lactate also revealed a significant ($P < .01$) increase. Strain influence showed stress prone swine glucose and lactate increases to be significant at the ($P < .01$) level, and fat strain Poland China swine glucose and lactate increased significantly ($P < .05$) in response to induced stress. The stress prone swine responded to stress with a significant ($P < .01$) decline in whole

blood pH, while blood pH remained relatively stable in the fat strain Poland China pigs. The stress prone swine possessed significantly higher ($P < .05$) sodium and ($P < .01$) potassium after stress than did the fat strain swine. No major strain or treatment effect was observed for plasma chloride.

4. Treatment with phenoxybenzamine and propranolol in relation to non-treated controls within each strain prior to induced stress resulted in the following characteristics after five minutes of induced physical exercise: phenoxybenzamine treated stress prone swine exhibited cutaneous blotching, tail and ear tremors, forced deep and irregular respiration, abnormal vocalization, hypertension, physical collapse, high plasma glucose, reduced plasma cortisol elevation, reduced plasma epinephrine, very high plasma lactate, substantial blood pH decline, and high plasma potassium. The phenoxybenzamine treated fat strain Poland China swine revealed minor cutaneous blotching and increase in respiration rate, no physical collapse, less magnitude in elevations of plasma cortisol, glucose and lactate, epinephrine and potassium, and a relatively stable blood pH. The propranolol treated stress prone swine exhibited an increased respiration rate, elevated plasma cortisol, glucose, lactate, and potassium but to a lesser degree than the phenoxybenzamine treated pigs. Also, a decline in plasma epinephrine and blood pH was observed but again to a lesser degree than the phenoxybenzamine treated stress prone swine. The propranolol treated fat strain swine exhibited no adverse physical appearances, displayed a minor increase in respiration in response to stress, had an elevation in plasma, cortisol, epinephrine, glucose, and lactate but of less magni-

tude than the phenoxybenzamine treated pigs. A relatively stable plasma potassium level and blood pH was observed.

5. The phenoxybenzamine stress prone swine exhibited chracteristics of anoxic acidosis and traumatic death with conditions simulating those of hypertensive microcirculatory failure leading to the onset of a shock-like syndrome.
6. Stress prone swine possessed significantly higher ($P < .05$) concentration of lactate in the post-mortem liver.
7. A significant ($P < .01$) time influence was observed in all M. longissimus tissue as lactate concentration, pH, and color were observed at zero, three, and 24 hours post-mortem.
8. The stress prone swine carcasses exhibited M. longissimus muscle with significantly higher ($P < .01$) concentration of lactate. Ham musculature with frequent occurrence of hemorrhage in the small vessels was observed in the carcasses of the stress prone swine.

BIBLIOGRAPHY

Addis, P. B., M. D. Judge, R. A. Pickett and H. W. Jones. 1965. Environmental factors associated with porcine adrenal size and muscle characteristics. Journal of Animal Science 24: 127-130.

Addison, T. 1849. On the constitutional and local effects of disease of the suprarenal capsules. London Medical Gazzett 1: 517-518.

Ahlquist, R. P. 1948. A study of adrenotropic receptors. American Journal of Physiology 153: 586-591.

Albertson, K. 1963. Variation in meat color and its cause in pigs. Nord Veterinary Medicine 15: 977-981.

Altura, B. M. 1966. Role of glycocorticords in local regulation of blood flow. American Journal of Physiology 211: 1393-1396.

Anderson, R. W., P. M. James, Jr., C. E. Bredenburg and R. M. Hardaway. 1967. Phenoxybenzamine in septic shock. Annuals of Surgery 165: 341-350.

Armstrong, D. 1969. Hageman Factor and the spontaneous human plasma - kinin generation occurring in homogeneous media. Activation and inactivation. Inflamation. Biochemistry and Drug Interaction. Excerpta Medica Foundation, Amsterdam.

Armstrong, D. 1970. Complement and shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 93-102. Plenum Press, New York.

Armstrong, D., G. L. Mills and F. Sicuteri. 1966. Physiological influences on the liberation of human plasmakinin at low temperature. Hypotensive Peptides. Springer-Verlag, New York, New York.

Armstrong, D. and J. W. Stewart. 1960. Spontaneous plasma kinin formation in human plasma collected during labour. Nature 188: 1193-1199.

Baez, S. and L. R. Orkin. 1963. Effect of anesthetics on the response of the microcirculation to circulating hormones. Anesthesiology 24: 568-579.

Baez, S., S. G. Srikantia and B. Burack. 1958. Dibenzyline protection against shock and preservation of hepatic ferritin systems. American Journal of Physiology 192: 175-182.

Baez, S., B. W. Zweifach, R. Pellon and E. Shorr. 1951. A renal factor in vascular response to hemorrhagic and traumatic shock. American Journal of Physiology 166: 658-665.

Bainbridge, F. A. and J. W. Trevan. 1917. Some actions of adrenaline upon the liver. Journal of Physiology 51: 460-468.

Barcroft, H. 1962. Circulation in skeletal muscle. Circulation. Handbook of Physiology 3: 1353-1385.

Barcroft, H. and H. Knozett. 1949. On the action of noradrenaline, adrenaline and isopropylnoradrenaline on the arterial blood pressure, heart rate and muscle blood flow in man. Journal of Physiology 110: 194-208.

Bartelstone, H. J. and P. A. Nasmyth. 1963. Vasopressin potentiation of catecholamine actions in dogs, cat and rat aortic strip. American Journal of Physiology 208: 754-762.

Basowitz, H. S., S. J. Korchin, D. Okin, M. S. Goldstein and H. Gussack. 1956. Anxiety and performance changes with a minimal dose of epinephrine. Arch Neural Psychiatrics (Chicago) 76: 98-105.

Bate-Smith, E. C. 1948. The physiology and chemistry of rigor mortis. In Advances in Food Research. Vol. 1. pp. 1-96. Academic Press, New York, New York.

Bave, A. E., D. G. Johnson and W. M. Parkins. 1966. Blood flow and oxygen consumption with adrenergic blockade in hemorrhagic shock. American Journal of Physiology 211(2): 354-360.

Bean, J. and M. Sidky. 1958. Intestinal blood flow as influenced by vascular and motor reactions to acetylcholine and CO_2. American Journal of Physiology 194: 512-518.

Bergan, J. J., E. D. Teixeira and J. Conn, Jr. 1967. Thoracic duct electrolytes during intestinal ischemia. Clinical Research 15: 416-425.

Berk, J. L. 1970. The treatment of shock with beta adrenergic blockade. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 303-306. Plenum Press, New York.

Berk, J. L., J. F. Hagen, W. H. Beyer and R. Niazmand. 1967. The effect of epinephrine on arteriovenous shunts in the pathogenesis of shock. Surgery, Gynecology, and Obstetrics 124: 347-355.

Berne, R. M. 1958. Effect of epinephrine and norepinephrine on coronary circulation. Circulation Research 6: 664-671.

Berry, H., J. G. Collier and J. R. Vane. 1970. The generation of kinins in the circulation of the dog during hypotension due to blood loss. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 153-158. Plenum Press, New York.

Best, C. H. and N. B. Taylor. 1961. The Physiological Basis of Medical Practice. (7th Ed.). The Williams and Wilkin Company, Baltimore.

Bing, R. J. and H. Ramos. 1962. The role of the heart in shock. Journal of the American Medical Association 181: 871-873.

Black, J. W., A. F. Crowther, F. G. Shanks, L. H. Smith and A. C. Dornhorst. 1964. A new adrenergic beta-receptor antagonist. Lancet i: 1080-1081.

Blalock, A. 1942. Original not available; cited in J. H. Block, C. H. Pierce and R. C. Lillehei. 1966. Acrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Block, J. H., C. H. Pierce and R. C. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Bohstedt, G. and R. H. Grummer. 1954. Salt poisoning of pigs. Journal of Animal Science 13: 933-939.

Bowman, W. C. 1959. A comparison between the vascular responses to adrenaline and noradrenaline in individual skeletal muscle of the cat. Journal of Pharmacy and Pharmacology 11: 104-119.

Braunsberg, H. and V. H. T. James. 1961. The determination of cortisol and corticosterone in blood. Journal of Clinical Endocrinology 21: 1146-1162.

Braunwald, E. 1965. Shock in myocardial infarction. American Heart Journal 38: 365-371.

Briskey, E. J. 1959. Some factors contributing to pork quality. Reciprocal Meat Conference Proceedings 12: 146-148.

Briskey, E. J., W. G. Hoekstra, R. W. Bray and R. H. Grummer. 1960. Comparison of certain physical and chemical characteristics of eight pork muscles. Journal of Animal Science 19: 214-225.

Briskey, E. J. and J. Wismer-Pedersen. 1961. Biochemistry of pork muscle structure. Journal of Food Science 26: 297-302.

Broder, G. and M. H. Weil. 1964. Excess lactate: An index of reversibility of shock in human patients. Science 143: 1457-1469.

Cabbold, A. F. and C. C. N. Voss. 1953. Responses of muscle blood vessels of intra-arterially and intravenously administered noradrenaline. Journal of Physiology 120: 105-112.

Cannon, W. B. 1923. Traumatic Shock. D. Appleton and Company, New York, New York.

Cannon, W. B. 1929. Bodily Changes in Pain, Hunger, Fear and Rage. Appleton Century-Crofts. New York, New York.

Cannon, W. B. 1934. Original not available; cited in J. H. Block, C. J. Pierce and R. E. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Carlo, P. 1970. The reticulo-endothelial system (RES) in traumatic shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 241-248. Plenum Press, New York.

Cassens, R. G., M. D. Judge, J. D. Sink and E. J. Briskey. 1965. Porcine adrenocortical lipids in relation to striated muscle characteristics. Experimental Biology and Medicine Society Proceedings 120: 854-856.

Celander, O. 1954. The range of control exercise by the sympathico-adrenal system. Acta Physiologica Scandinavia 32, Supplement 116.

Cohn, J. M. 1966. Treatment of shock. General Practitioner 24(2): 78-85.

Cooper, C. C., R. G. Cassens and E. J. Briskey. 1969. Capillary distribution and fiber characteristics in skeletal muscle of stress susceptible animals. Journal of Food Science 34: 299-302.

Copeland, G. D. 1967. Beta adrenergic blockade. Journal of the Tennessee Medical Association 60(9): 946-947.

Crile, G. H. 1899. An Experimental Research into Surgical Shock. Lippincott, Philadelphia, Pennsylvania.

Crowell, J. W. 1970. Oxygen transport in the hypotensive state. Federation Proceedings 29: 18 8-1853.

Crowell, J. W. and A. C. Guyton. 1962. Further evidence favoring a cardiac mechanism in irreversible hemorrhagic shock. American Journal of Physiology 203: 248-252.

Crowell, J. W. and W. L. Read. 1955. In vivo coagulation- a probable cause of irreversible shock. American Journal of Physiology 183: 565-569.

Crowell, J. W. and E. E. Smith. 1964. Oxygen deficit and irreversible hemorrhagic shock. American Journal of Physiology 206: 313-319.

Dale, H. H. 1929. Some chemical factors in the control of the circulation. Lancet 1: 1179-1183.

Daugherty, R. M., Jr., J. B. Scott, J. M. Dabney and F. J. Haddy. 1967. Local effects of O_2 and CO_2 on limb, renal and coronary vascular resistance. American Journal of Physiology 213: 1102-1110.

Davies, R. O., W. M. Cameron, N. K. Hollenberg and A. E. Thomson. 1965. Original not available; cited in J. H. Block, C. J. Pierce and R. E. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Detar, R. and D. F. Bohr. 1968. Oxygen and vascular smooth muscle contraction. American Journal of Physiology 214: 241-244.

Dhar, H. L. 1970. Effect of varying blood sugar level in anaphylatic shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 189-197. Plenum Press, New York.

Dhar, H. L., R. K. Sanyal and G. B. West. 1967. The relationship of the blood sugar level to the severity of anaphylactic shock. British Journal of Pharmacology 31: 351-363.

Dias da Silva, W. and I. H. Lepow. 1965. Anaphylatoxin formation by purified human c'1 esterase. Journal of Immunology 95: 1080-1089.

Dias da Silva, W. and L. H. Lepow. 1967. Complement as a mediator of inflammation. II. Biological properties of anaphylatoxin prepared with purified components of human complement. Journal of Experimental Medicine 125: 921-932.

Dietzman, R. H., J. H. Block and R. C. Lillehei. 1967. Treatment of shock. General Practitioner 36: 3, 135-141.

Dutta, S. N. and H. L. Dhar. 1958. Carbohydrate metabolism and anaphylaxis. Asseptic Allergy and Applied Immunology 1: 15-28.

Eckenhoff, J. E. and L. H. Cooperman. 1965. The clinical application of phenoxybenzamine in shock and vasoconstrictive states. Surgery, Gynecology and Obstetrics 121: 483-490.

Elliot, T. R. 1904. On the action of adrenalin. Journal of Physiology 31: xx-xxi.

Elmadjian, F., J. M. Hope and E. T. Lamson. 1958. Excretion of epinephrine and norepinephrine under stress. Recent Progress in Hormone Research 14: 513-553.

Erdos, E. G. 1963. In Kontas, H. A., J. H. Magee, W. Shapiro and J. L. Patterson. 1964. General and regional circulatory effects of synthetic bradykinin in man. Circulation Research 14: 351-356.

Erlanger, J. and H. S. Gasser. 1919. Studies in secondary traumatic shock. II. Shock due to mechanical limitation of blood flow. III. Circulatory failure due to adrenaline. American Journal of Physiology 49: 151-173, 345-376.

Fine, J. 1954. The Bacterial Factor in Traumatic Shock. Charles C. Thomas, Springfield, Illinois.

Fleisch, A. et al. 1932. Original not available; cited in H. Wilkins, N. Back, R. Steger and J. Karn. 1970. The influence of blood pH on peripheral vascular tone: possible role of proteases and vasoactive polypeptides. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 201-214. Plenum Press, New York.

Folkow, B. 1962. Shock: Its pathogenesis and treatment. Nervous adjustment of the vascular bed with special reference to patterns of vasoconstrictor fiber discharge. Ciba Symposium. Springer-Verlag, Heidelberg.

Folkow, B. J. and B. Uunas. 1948. Action of adrenaline, noradrenaline and some other sympathomimetic drugs on muscular, cutaneous and splanchnic vessels of cat. Acta Physiology 15: 412-416.

Forrest, J. C., J. A. Will, G. Schmidt, M. D. Judge and E. J. Briskey. 1968. Homeostasis in animals (Sus domesticus) during exposure to a warm environment. Journal of Applied Physiology 24: 33-39.

Fox, R. H., R. Goldsmith, D. J. Kidd and G. P. Lewis. 1961. Bradykinin as a vasodilator in man. Journal of Physiology 157: 589-602.

Frank, E. D., H. A. Frank, S. Jacob and J. Fine. 1962. Hepatic blood flow in experimental hemorrhagic shock. American Journal of Physiology 202: 7-11.

Frankenhauser, M., G. Jarpe and G. Matell. 1961. Effects of intravenous infusions of adrenaline and noradrenaline on certain psychological and physiological functions. Acta Physiologlica Scandinavia 51: 175-186.

Freeman, N. E. 1933. Decrease in blood volume after prolonged hyperactivity of the sympathetic nenous system. American Journal of Physiology 103: 185-202.

Freis, E. D. 1960. Hemodynamics of hypertension. Physiological Review 40: 27-36.

Frey, E. K. 1930. Original not available; cited in H. Wilkins, N. Back, R. Steger and J. Karn. 1970. The influence of blood pH on peripheral vascular tone: Possible role of proteases and vasoactive polypeptides. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 201-214. Plenum Press, New York.

Fritz, I. and K. Levine. 1951. Action of adrenal cortical steroids and norepinephrine on vascular responses of stress in adrenalectomized rats. American Journal of Physiology 165: 456-465.

Fukuda, T. and Y. I. Fukuda. 1969. Mechanism of anti-shock effect of glucocorticoid in hemorrhagic shock in rabbit. Japanese Journal of Physiology 19: 682-690.

Fukuda, T., H. Okuma and N. Hata. 1967. Epinephrine shock, its relation to plasma epinephrine level and the mechanism of its protection by glucocorticoid. Japanese Journal of Physiology 17: 746-754.

Gelin, L. E. 1956. Studies in the anemia of injury. 1956. Acta Chiropractica Scandinavia Supplement 210.

Gellhorn, E. 1943. Autonomic regulations. Interscience, New York, New York.

Gillman, P. M. S. and B. N. C. Prichard. 1965. Use of propranolol in angina pectoris. British Medical Journal 1965: 337-339.

Glenn, E. M., B. J. Bowman, R. B. Boyer and C. E. Meyer. 1961. Hydrocortisone and some of its effects on intermediary metabolism. I. In vivo studies. Endocrinology 68: 386-391.

Glenn, E. M., W. L. Miller and C. A. Schlagel. 1963. Metabolic effects of adrenocortical steroids in vivo and in vitro: relationships to anti-inflammatory effects. Recent Progress in Hormone Research 19: 107-200.

Goldspink, G. and J. V. McLaughlin. 1964. Studies on pig muscle. 3. The effect of temperature on the solubility of the sarcoplasmic proteins in relation to colour changes in post-rigor muscle. Irish Journal of Agricultural Research 3: 9-15.

Gourzis, J. T., M. W. Hollenberg and M. J. Nickerson. 1961. Original not available; cited in J. H. Block, C. J. Pierce and R. E. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Gourzis, J. T. and M. Nickerson. 1965. Intraorgan blood flow distribution in shock. In Shock and Hypotension. Pp. 289-294. Grune and Stratton, Inc., New York, New York.

Green, H. D. and J. H. Kepchar. 1959. Control of peripheral resistance in major systemic vascular beds. Physiology Review 39: 617-686.

Gross, F. 1960. Renal and extrarenal actions of aldosterone and its influence on sodium transport. First International Congress of Endocrinology, Copenhagen, Symposium III, Lecture 2: 61-63.

Gross, F. 1961. Renal and extrarenal actions of aldosterone. Experientia 17: 57-67.

Gunther, H. and A. Schweiger. 1966. Changes in the concentration of lactic acid and free sugars in post-mortem samples of beef and pork muscle. Journal of Food Science 31: 300-308.

Guyton, A. C. and J. W. Crowell. 1961. Dynamics of the heart in shock. Federation Proceedings 20, Supplement 9: 51-60.

Haas, M. C. and L. J. Bratzler. 1965. Determination of myoglobin oxygenation rates in pork, beef, and lamb by Munsell and reflectance colorimetry. Journal of Food Science 30: 64-68.

Hahn, F., A. Lange and H. Giertz. 1954. Anaphylaktoide reaktionen durch kunstliche blutersatzstoffe. Archiv fur Experimentelle Pathologie und Pharmakogie 222: 603-612.

Hahn, F. and Oberdorf, A. 1950. Antihistaminica und anaphylaktoide reaktionen. Zeitschrift fur. Immunologische-forschung 107: 528-533.

Halpern, B. N., B. Benacerraf and M. Briot. 1952. The roles of cortisone, desoxycorticosterone and adrenaline in protecting adrenalectomized animals against haemorrhagic, traumatic, and histamine shock. British Journal of Pharmacology 7: 287-297.

Halpern, B. N. and D. R. Wood. 1950a. Mise en evidence de l'action anti-toxique d'un antihistaminique do synthese vis-a vis de l'histamine chez la Souris par la surrenalectomie. Academie Des Sciences 230: 138-140.

Halpern, B. N. and D. R. Wood. 1950b. The action of promethazine (phenergan) in protecting mice against death due to histamine. British Journal of Pharmacology and Chemotherapy 5: 510-516.

Hamm, R. 1960. Biochemistry of meat hydration. Advances in Food Research 10: 355-361.

Hardaway, R. M., A. M. James, Jr., R. W. Anderson, C. E. Bredenberg and R. L. West. 1967. Intensive study and treatment of shock in man. Journal of the American Medical Association 199: 779-790.

Hardaway, R. M. and D. A. Johnson. 1963. Unified theory of shock. American Surgeon 29: 292-298.

Hart, P. C. 1961. Determination of the color of meat by measuring the extinction value. Tydschr. Diergeniesk 86: 340-346.

Harvey, W. R. 1960. Least Squares Analysis of Data with Unequal Subclass Numbers. U.S.D.A. Pub. ARS-20-8.

Heimbecker, R. O. and W. G. Bigelow. 1950. Intravascular agglutination of erythrocytes (sludged blood) and traumatic shock. Surgery 28: 461-473.

Henry, M., J. D. Romani and L. Joubert. 1958. Myopathic exudative depigmentation du porc Maladie de l'adaption Essai pathogenique et consequences pratques. Revue de Pathologie Generale et de Physiologie Clinique 696: 355-398.

Hill, J. B. and G. Kessler. 1961. An automated determination of glucose utilizing a glucose oxidase-peroxide system. Journal of Laboratory and Clinical Medicine 57: 970-980.

Hilton, S. M. 1962. Local mechanisms regulating peripheral blood flow. Physiological Review 42: 265-275.

Hinshaw, L. B., M. M. Jordan and J. A. Vick. 1961. Histamine release and endotoxin shock in the primate. Journal of Clinical Investigation 40: 1631-1637.

Hinshaw, L. B., J. A. Vick, M. M. Jordan and L. E. Wittmers. 1962. Vascular changes associated with the development of irreversible endotoxin shock. American Journal of Physiology 202: 103-110.

Hirshfeld, J. W., Jr. and C. Fell. 1969. Changes in regional blood content during hemorrhagic shock in dogs. American Journal of Physiology 216: 2, 380-385.

Hochella, N. J. and S. Weinhouse. 1965. Automated lactic acid determination in serum and tissue extracts. Analytical Biochemistry 10: 304-317.

Hohorst, H. J. 1962. L- (+) lactate determination with lactic dehydrogenase and DPN. In H.V. Bergmeyer, Ed. Methods of Enzymatic Analysis. Pp. 266-270. Academic Press, New York, New York.

Houck, J. C. and J. A. Gladner. 1970. Proposed mechanisms for the ameliorative effects of corticosteroid in shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 125-132. Plenum Press, New York.

Huckabee, W. E. 1958a. Relationships of pyruvate and lactate during anaerobic metabolism: I. Effects of infusion of pyruvate or glucose and of hyperventilation. Journal of Clinical Investigation 37: 244-254.

Huckabee, W. E. 1958b. Relationships of pyruvate and lactate during anaerobic metabolism: II. Exercise and formation of oxygen debt. Journal Clinical Investigation 37: 255-262.

Jersild, A. T. and W. S. Thomas. 1931. The influence of adrenal extract on behavior and mental efficiency. American Journal of Psychology 43: 447-456.

Jones, R. T. and W. D. Blake. 1958. Dynamics of epinephrine destribution in the dog. American Journal of Physiology 193: 365-372.

Judge, M. D., E. J. Briskey, R. G. Cassens, J. C. Forrest and R. K. Meyer. 1968. Adrenal thyroid function in stress-susceptible pigs (Sus domesticus). American Journal of Physiology 214: 146-151.

Judge, M. D., E. J. Briskey and R. K. Meyer. 1966. Endocrine related post-mortem changes in porcine muscle. Nature 212: 287-288.

Judge, M. D., R. G. Cassens and E. J. Briskey. 1967. Muscle properties of physically restrained stressor-susceptible and stressor-resistant porcine animal. Journal of Food Science 32: 565-567.

Judge, M. D., J. C. Forrest, J. D. Sink and E. J. Briskey. 1968. Endocrine related stress response and muscle properties of swine. Journal of Animal Science 27: 1247-1253.

Kastenschmidt, L. R. and E. J. Briskey. 1966. Metabolic intermediates in skeletal muscles with fast and slow rates of post-mortem glycolysis. Nature 212: 288-393.

Kayaalp, S. O. and B. K. Kiran. 1966. Mechanism of a sympathomemetric action of propranolol in dog. British Journal of Pharmacology and Chemotherapeutics 28: 15-22.

Kern, W., D. S. Mierzwiak, R. W. Meyers and J. H. Mitchell. 1968. Effects of acute lactic acidosis on left ventricular performance. American Journal of Physiology 214(6): 1352-1359.

Kester, N. C., A. W. Richardson and H. D. Green. 1952. Effect of controlled hydrogen-ion concentration on peripheral vascular tone and blood flow in innervated hind leg of the dog. American Journal of Physiology 169: 678-687.

Kilburn, K. H. 1966. Muscle origin of elevated plasma potassium during exercise. Journal of Applied Physiology 21: 675-678.

Knisely, M. H., T. S. Eliot and E. H. Block. 1945. Sludged blood in traumatic shock, microscopic observations and precipitation and agglutination of blood flowing through vessels in crushed tissues. Archives of Surgery 51: 220-236.

Kontos, H. A., J. H. Magee, W. Shapiro and J. L. Patterson. 1964. General and regional circulatory effects of synthetic bradykinin in man. Circulation Research 14: 351-356.

Kontos, H. A., H. P. Mauck, Jr. and J. L. Patterson, Jr. 1965. Mechanism of reactive hyperemia in limbs of anesthetized dogs. American Journal of Physiology 209: 1106-1114.

Kontos, H. A. and J. L. Patterson, Jr. 1964. Carbon dioxide as a major factor in the production of reactive hyperemia in the human forearm. Clinical Sciences 27: 143-154.

Kontos, H. A., D. W. Richardson and J. L. Patterson, Jr. 1966. Blood flow and metabolism of forearm muscle in man at rest during sustained contraction. American Journal of Physiology 211: 869-876.

Krogh, A. 1929. The Anatomy and Physiology of Capillaries. Yale University, New Haven, Conn.

Landis, C. 1935. The effect of the injection of adrenaline on complex muscular activity. Journal of Comparative Psychology 19: 113-117.

Lanier, B. S., H. D. Green, J. Hardaway, H. D. Johnson and W. B. Donald. 1953. Fundamental differences in the reactivity of the blood vessels in skin compared with those in muscle. Circulation Research 1: 40-48.

Lawrie, R. A. 1958. Physiological stress in relation to dark-cutting beef. Journal of the Science of Food and Agriculture 9: 721-729.

Lazarus, R. S., J. Deese, and S. F. Osler. 1952. The effects of psychological stress upon performance. Psychology Bulletin 49: 293-317.

Lefer, A. M. 1970. Roles of a myocardial depressant factor in the pathogenesis of circulatory shock. Federation Proceedings 29: 1836-1847.

Lefer, A. M., R. Cowgill, F. F. Marshall, L. M. Hall and E. D. Brand. 1967. Characterization of a myocardial depressant factor present in hemorrhagic shock. American Journal of Physiology 213: 492-498.

Lefer, A. M. and R. L. Verrier. 1970. Role of corticosteroids in the treatment of circulatory collapse states. Clinical Pharmacology and Therapeutics 11: 630-655.

Lesh, T. A. and C. F. Rothe. 1969. Sympathetic and hemodynamic effects on capacitance vessels in dog skeletal muscle. American Journal of Physiology 217: 3, 819-827.

Lewis, R. B. and E. Freytag. 1951. Use of cortisone in treatment of experimental frostbite. Proceedings of the Society of Experimental Biology and Medicine 77: 816-824.

Lewis, D. H. and S. Mellander. 1962. Competitive effects of sympathetic control and tissue metabolites on resistance and capacitance vessels and capillary filtration in skeletal muscle. Acta Physiological Scandinavia 56: 162-188.

Lillehei, R. C. 1957. The intestinal factor in irreversible hemorrhagic shock. Surgery 42: 1043-1954.

Lillehei, R. C. 1960. An Inquiry into the Nature of Experimental Shock. Doctoral Thesis, University of Minnesota, Minneapolis, Minnesota.

Lillehei, R. C., J. K. Longerbeam, J. H. Block and W. G. Manax. 1964. The modern treatment of shock based on physiologic principles. Clinical Pharmacology and Therapeutics 5: 63-101.

Lillehei, R. C., J. K. Longerbeam, J. H. Block and W. G. Manax. 1965. Adrenergic blocking drugs in the treatment of shock. Cardiovascular Drug Therapy. Grune and Stratton Co , Philadelphia, Penn.

Lillehei, R. C., J. K. Longerbeam and J. C. Rosenberg. 1962. Shock: Its pathogenesis and treatment. Ciba Symposium. Springer-Verlag, Heidelberg.

Lindner, H. R. 1964. Comparative aspects of cortisol transport: lack of firm binding to plasma proteins in domestic ruminants. Journal of Endocrinology 28: 301-316.

Lohse, B. and A. Pfau. 1964. Ein handliches fleisch-farben-ver gleishsphotometer fur den praktischen schlachtbetrub sonderdruck aus die fleishchwirtshaft 44. Supplement 16, Heft 7: 658-664.

Longerbeam, J. K., R. C. Lillehei, W. R. Scott and J. C. Rosenberg. 1962. Visceral factors in shock. Journal of the American Medical Association 181: 878-883.

Ludvigsen, J. 1953. "Muscle degeneration" in hogs (preliminary report). International Veterinary Congress Proceedings 15, Vol. 1, part 1: 602-604.

Ludvigsen, J. 1957. On the hormonal regulation of vasomotor reactions during exercise with special reference to the action of adrenal cortical steroids. Acta Endocrinologica 26: 406-416.

Ludvigsen, J. 1968. The effect of adrenal cortical steroids in PEM-susceptible pigs. International Symposium on Meat Quality, Zeist, The Netherlands, May, 1968.

McKay, D. G., R. M. Hardaway, F. G. Wohle, Jr., and R. M. Hall. 1955. Experimental pseudomembranous entercolitis. American Medical Association Archives of Internal Medicine 95: 779-787.

McLaughlin, J. V. and G. Goldspink. 1963. Post-mortem changes in the colour of pig longissimus dorsi muscle. Nature 198: 584-589.

Malcolm, J. D. 1905. The condition of the blood vessels during shock. Lancet 2: 573-579.

Manger, W. M., G. G. Hahas, D. Hassam, D. V. Habif and E. M. Papper. 1962. Original not available; cited in R. C. Lillehei, J. K. Longerbeam and J. C. Rosenberg. 1962. Shock: Its pathogenesis and treatment. Ciba Symposium. Springer-Verlag, Heidelberg.

Marple, D. N. 1968. Effects of ante-mortem stress and hydrocortisone on porcine plasma and muscle characteristics. Master's thesis, Iowa State University of Science and Technology, Ames, Iowa.

Marple, D. N., D. G. Topel and C. Y. Matsushima. 1969. Influence of induced adrenal insufficiency and stress on porcine plasma and muscle characteristics. Journal of Animal Science 29: 882-886.

Maxwell, G. M., R. B. Elliott and G. M. Kneebone. 1962. Effects of bradykinin on the systemic and coronary vascular bed of the intact dog. Circulation Research 10: 359-363.

Minaire, Y. 1967. Au su jet du dosage automatique de l'acide lactique. In E. Kaweran, H. Jerome and D. Stamm, eds. Technicon Symposia; Automation in analytical chemistry, 1966. Vol. 2. Pp. 151-154. Medical Incorporated, White Plains, New York.

Mlynaryk, P., R. R. Gillies, B. E. P. Murphy and C. J. Pattee. 1962. Cortisol production rates in obesity. Journal of Clinical Endocrinology 22: 587-593.

Molnar, J. I., J. B. Scott, E. D. Frohlich and F. J. Haddy. 1962. Local effects of various anions and H^+ on dog limb and coronary vascular resistances. American Journal of Physiology 203: 125-132.

Moses, M. L., R. C. Camishion, T. Kouichi, L. Pierocci and A. L. Davis. 1965. Effect of corticosteroid on the acidosis of prolong cardiopulmonary bypass (P). Circulation Supplement II: 155-156.

Motsay, G. J., A. Alho, T. Jaeger, R. H. Dietzman and R. C. Lillehei. 1970. Effects of corticosteroid on the circulation in shock: experimental and clinical results. Federation Proceedings 29: 1861-1873.

Murphy, B. E. P. 1967a. The determination of plasma levels of corticoids and their diagnostic significance. In E. Bajusz and S. Karger, eds. An Introduction to Clinical Neuroendocrinology. Pp. 164-185. Basel, New York.

Murphy, B. E. P. 1967b. Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. Journal of Clinical Endocrinology 27: 973-990.

Murphy, B. E. P., W. Engelberg and C. J. Pattee. 1963. Simple method for the determination of plasma corticoids. Journal of Clinical Endocrinology 23: 293-300.

Nahas, G. G. and C. Payart. 1967. Effect of arterial pH alteration on metabolic activity of norepinephrine. American Journal of Physiology 212: 765-772.

Nakano, J. and T. Kusakari. 1965. Effect of propranolol on the peripheral circulation. Proceedings of the Society of Experimental Biological Medicine 120: 516-519.

Nakano, J. and T. Kusakari. 1966. Effect of propranolol on the peripheral vascular bed. Nature 209: 923-924.

Neaverson, M. A. 1966. Metabolic acidosis in acute myocardial infarction. British Medical Journal 2: 383-385.

Nelson, W., H. S. Mayerson, J. H. Clark and C. Lyons. 1947. Studies of blood volume in the tetralogy of fallot and in other types of congenital heart disease. Journal of Clinical Investigation 25: 860-868.

Nickerson, M. 1963. Sympathetic blockade in the therapy of shock. American Journal of Cardiology 12: 619-623.

Nickerson, M. 1965. Drugs inhibiting adrenergic nerves and structures innervated by them. In L. S. Goodman and A. Gilman, eds. The Pharmacological Basis of Therapeutics. Ch. 26. Pp. 546-577. The Macmillan Company, New York, New York.

Nickerson, M. and S. A. Carter. 1959. Protection against acute trauma and traumatic shock by vasodilators. Canadian Journal of Biochemistry and Physiology 37: 1161-1168.

Nickerson, M. and J. T. Gourzis. 1962. Blockade of sympathetic vasoconstriction in the treatment of shock. Journal of Trauma 2: 399-411.

Nichols, C. T. and F. H. Tyler. 1967. Diurnal variation in adrenal cortical function. Annual Review of Medicine 18: 313-315.

Novelli, G. P., C. Cortesini and E. Pagni. 1970. The role of splanchnic adrenergic vasoconstriction in the development of irreversibility of hemorrhagic shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 103-106. Plenum Press, New York.

Overman, R. R. and S. C. Wong. 1947. The contributory role of afferent nervous factor on experimental shock: sublethal hemorrhage and sciatic nerve stimulation. American Journal of Physiology 148: 289-306.

Page, I. H. and J. W. McCubbin. 1956. Physiology of arterial hypertension. In W. F. Hamilton and Phillip Dow, eds. Handbook of Physiology. Section 2: Circulation. Vol. 3. Pp. 2163-2184. American Physiological Society, Washington, D.C.

Paldino, R. L., C. Hyman and J. Lenthall. 1962. Bradykinin-induced increase in total and effective blood flow in skeletal muscle. Circulation Research II: 847-852.

Payart, C. and G. G. Nahas. 1966. Inhibition of catecholamine induced calorigenesis and lipolysis by hypercapnic acidosis. American Journal of Physiology 211(1): 161-168.

Peretz, D. I., H. M. Scott and J. Duff. 1965. Significance of lactiacidemia in the shock syndrome. Annuals of New York Academy of Science 119: 1133-1148.

Perlroth, M. G. and D. C. Harrison. 1969. Cardiogenic shock: a review. Clinical Pharmacology and Therapeutics 10: 449-467.

Pettigrew, J., Jr. 1969. Blood carbohydrate levels in the neonatal pig. Master's thesis, Iowa State University of Science and Technology, Ames, Iowa.

Prichard, B. N. C. and P. M. S. Gillman. 1964. Use of propranolol (Inderal) in treatment of hypertension. British Medical Journal ii: 725-727.

Ramey, E. R. and M. S. Goldstein. 1957. The adrenal cortex and the sympathetic nervous system. Physiology Review 155-195.

Ramey, E. R., M. S. Goldstein and R. Levine. 1951. Action of norepinephrine and adrenal cortical steroids on blood pressure and work performance of adrenalectomized dogs. American Journal of Physiology 165: 450-455.

Raynor, R. R., L. D. MacLean and E. Grim. 1960. Intestinal tissue blood flow in shock due to endotoxin. Circulation Research 8: 1212-1217.

Remington, J. W., W. F. Hamilton, G. H. Boyd, Jr., W. F. Hamilton, Jr. and H. M. Caddell. 1950. Role of vasoconstriction in the response of the dog to hemorrhage. American Journal of Physiology 161: 116-124.

Robin, M. and A. Saifer. 1965. Determination of glucose in biological fluids with an automated enzymatic procedure. Clinical Chemistry 11: 840-845.

Roch e Silva, M. 1954. Anaphylatoxin and histamine release. Quarterly Reviews of Allergy 8: 220-235.

Roch e Silva, M. 1970. Participation of the kinin system in different kinds of shock. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 135-152. Plenum Press, New York.

Roch e Silva, M., O. Bier and M. Aronson. 1951. Histamine release by anaphylatoxin. Nature 168: 465-469.

Romanul, F. C. A. 1965. Capillary supply and metabolism of muscle fibers. Archives of Neurology 12: 497-509.

Ross, J., Jr., G. A. Kaiser and F. J. Klocke. 1964. Observations on the role of diminished oxygen tension in the functional hyperemia of skeletal muscle. Circulation Research 15: 473-484.

Rothe, C. F. 1968. Oxygen deficit in hemorrhagic shock in dogs. American Journal of Physiology 214(3): 436-442.

Rudko, M. and F. J. Haddy. 1965. Venous plasma (K^+) during reactive hyperemia in skeletal muscle. The Physiologist 8: 264-265.

Sarnoff, S. J., R. B. Case, P. E. Waithe and J. P. Isaacs. 1954. Original not available; cited in R. C. Lillehei, J. K. Longerbeam and J. C. Rosenberg. 1962. Shock: Its pathogenesis and treatment. Ciba Symposium. Springer-Verlag, Heidelberg.

Sayre, R. N., B. Kiernat and E. J. Briskey. 1964. Processing characteristics of porcine muscle related to pH and temperature during rigor mortis development and to gross morphology 24 hours post-mortem. Journal of Food Science 29: 175-180.

Schauer, A., L. Gielow and G. Geissel. 1970. Behavior of histidine decarboxylase (HDC). In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 59-72. Plenum Press, New York.

Schneider, C. L. 1970. Extrinsic versus intrinsic coagulation fibrinolysis: in the pathophysiology of shock and exsanguination diathesis. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 73-92. Plenum Press, New York.

Schroder, J., B. Lohse and A. Pfau. 1965. Suggestions of objective valuation of meat character in pigs with "Fahellpho-Mariensee". Fleischwirtschaft 45: 228-237.

Schumer, W. 1968. Localization of the energy pathway block in shock. Surgery 64: 55-62.

Schumer, W. and R. Sperling. 1968. Shock and its effect on the cell. Journal of the American Medical Association 205: 215-219.

Schweigert, B. S. 1956. Chemistry of meat pigments. Chemical nature of myoglobin and related compounds. American Meat Institute Foundation Conference Proceedings 8: 61-73.

Scrutton, M. C. and M. F. Utter. 1968. The regulation of glycolysis and gluconeogenesis in animal tissues. Annual Review of Biochemistry 37: 249-302.

Seal, U. S. and R. P. Doe. 1963. Corticosteroid-binding globulin: species distribution and small scale purification. Endocrinology 73: 371-376.

Sechzer, P. H., L. D. Egbert, H. W. Linde, D. Y. Cooper, R. D. Dripps and H. L. Price. 1960. Effect of CO_2 inhalation on arterial pressure, ECG and plasma catecholamine and 17-hydroxicorticosteroids in normal man. Journal of Applied Physiology 15: 454-458.

Selkurt, E. E. 1946. Renal blood flow and renal clearance during hemorrhagic shock. American Journal of Physiology 145: 699-709.

Selkurt, E. E. 1959. Intestinal ischemic shock and the protective role of the liver. American Journal of Physiology 196: 281-283.

Selkurt, E. E. 1970. Status of investigative aspects of hemorrhagic shock. Federation Proceedings 29: 1832-1835.

Selkurt, E. E., R. S. Alexander and M. B. Patterson. 1947. The role of the mesenteric circulation in the irreversibility of hemorrhagic shock. American Journal of Physiology 149: 732-743.

Selye, H. 1949. Textbook of Endocrinology. 2nd ed. Acta Endocrinologica, Montreal.

Selye, H. 1950. The physiology and pathology of exposure to stress. Acta Inc. Medical Publishers, Montreal.

Shagal, D. I. and G. L. Shraiberg. 1964. Adrenal cortex in myopathics, functional state. Federation Proceedings 23: 1253-1262.

Shanks, R. G. 1966. The effect of propranolol on the cardiovascular responses to isoprenaline, adrenaline and noradrenaline in the anaesthetised dog. British Journal of Pharmacology and Chemotherapy 26: 322-333.

Shanks, R. F. 1967. The peripheral vascular effects of propranolol and related compounds. British Journal of Pharmacology and Chemotherapy 29: 204-217.

Shayer, R. W. 1963. Induced synthesis of histamine, microcirculatory regulation and the mechanism of action of the adrenal glucocorticoid hormones. Progress in Allergy 7: 187-212.

Sheehan, H. L. 1948. Shock in obstetrics. Lancet 1: 1-22.

Shurtshin, A., S. Rodbard and L. N. Katz. 1948. Inhibition of epinephrine action in severe hypoxemia. American Journal of Physiology 152: 623-632.

Sicuteri, F. 1967. Vasoneuroactive substances and their implications in vascular pain. Research and Clinical Study. Headache. S. Karger I, 6-12.

Sicuteri, F., P. L. Del Bianco and M. Fancuillacci. 1970. Kinins in the pathogenesis of cardiogenic shock and pain. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 315-322. Plenum Press, New York.

Sicuteri, F., M. Fanciullacci, G. Franchi and P. L. Del Bianco. 1965. Serotonin-bradykinin potentiation on receptors in man. Life Science 4: 309-322.

Sigma Chemical Company. 1965. The determination of L(+) lactic acid in blood plasma or other fluids at 340mμ. Sigma Chemical Technical Bulletin No. 825-uv.

Skinner, N. S. and W. J. Powell, Jr. 1967. Action of oxygen and potassium on vascular resistance of dog skeletal muscle. American Journal of Physiology 212: 533-540.

Smuddy, F. G., D. Segel and J. Fine. 1958. In J. H. Block, C. H. Pierce and R. C. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Snedecor, G. W. and W. G. Cochran. 1967. Statistical Methods. 6th ed. Iowa State University Press, Ames, Iowa.

Soffer, L. J., R. I. Dorfman and J. L. Gabrilove. 1961. The Human Adrenal Gland. Lea and Febiger, New York.

Steinberg, H. 1959. Effects of drugs on performance and incentives. In Symposium on Quantitative Methods in Human Pharmacology and Therapeutics. Pergamon Press, London.

Steinhauf, D., F. K. Weiss and J. H. Weniger. 1966. Ein weiterer beitrag aur methodik der helligkeits-measung beim schweinedfleisch. Die flaschwert shaft 46: Heft 1: 39-52.

Steinhauf, D., J. H. Weniger and K. H. Hoppenbrock. 1969a. Stress resistance as a production character in the pig. Sonderdrucke aus "Zuchtungskunde" Band 41, Heft 21: 93-111.

Steinhauf, D., J. H. Weniger and C. Augustine. 1969b. Stress resistance as a production character in the pig. Sonderdrucke aus "Zuchtungskunde" Band 41, Heft 5: 335-345.

Stickney, J. C. and E. J. Van Liere. 1953. Acclimatization of low oxygen tension. Physiology Review 33: 13-34.

Sukhnandan, R. and A. P. Thal. 1965. The effect of endotoxin and vasoactive agents on dibenzyline-pretreated lungs. Surgery 58: 185-196.

Swingle, W. W. and J. W. Remington. 1944. The role of the adrenal cortex in physiological processes. Physiological Reviews 24: 89-127.

Sybesma, W. and G. Eckelenboom. 1969. Malignant hyperthermia syndrome in pigs. Netherland Journal of Veterinary Science 2: 155-160.

Sybesma, W. and J. G. van Logtestyn. 1966. Pre-slaughter temperature and its effect on the post-mortem metabolism in pig muscle. XIIth European Meeting of Meat Research Workers at Sandjeford.

Technicon Corporation. 1965a. Lactic acid. Technicon Auto Analyzer Methodology N-56.

Technicon Corporation. 1965b. Lactic acid. Technicon Auto Analyzer Methodology N-206.

Thorn, G. M., M. Clinton, Jr., B. M. Davis and R. A. Lewis. 1945. Effect of adrenal cortical hormone therapy on altitude tolerance. Endocrinology 36: 381-390.

Topel, D. G., R. A. Merkel and J. Wismer-Pedersen. 1967. Relationships of plasma 17 hydroxycorticosteroid levels of some physical and biochemical properties of porcine muscle. Journal of Animal Science 26: 311-315.

Topel, D. G., E. J. Bichnell, K. S. Preston, L. L. Christian and C. Y. Matsushina. 1968. Procine stress syndrome. Modern Veterinary Practice 49: 40-60.

Topel, D. G. 1968a. Endocrine influence on the micro-circulatory system. Reciprocal Meat Conference 21: 194-203.

Topel, D. G. 1968b. Relation of plasma glucocorticoid levels to some physical and chemical properties of porcine muscle and the porcine stress syndrome. International Symposium on Meat Quality, Zeist, Holland, May 6-10.

Turner, C. D. 1960. General Endocrinology. 3rd ed. W. B. Sanders Co., Philadelphia, Pa.

Ullrey, D. E., E. R. Miller, B. E. Brent, B. L. Bradly and J. A. Hoefer. 1967. Swine hematology from birth to maturity. IV Serum Ca, Mg, Na, K, Cu, Zn and inorganic phosphorus. Journal of Animal Science 26: 1024-1029.

Ulrych, M., E. D. Frohlich, H. P. Dustan and I. H. Page. 1968. Immediate hemodynamic effects of beta adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation 37: 411-416.

Valori, C., C. A. Brunori, V. Renzini and L. Corea. 1970. Improved procedure for formation of epinephrine and norepinephrine fluorophors by the trihydroxyindole reaction. Analytical Biochemistry 33: 158-167.

Van Harrveld, A., C. H. Ellis and F. J. Wolfgram. 1952. An analysis of the cardiovascular action of levo-epinephrine and levo-norepinephrine. Archives of International Physiology 60: 421-440.

Van Loos, A., A. Surtshin and L. N. Katz. 1948. Nature of the two pressor responses to acute hypoxemia with some observations on the role of the adrenals in hypoxia. American Journal of Physiology 154: 397-416.

Vick, J. A., H. P. Ciuchta, J. H. Merickel and E. O. Lindseth. 1965. Vasodilation therapy in acute hemorrhagic shock. Circulation Research 16: 58-64.

Visscher, M. D. 1958. Original not available; cited in R. C. Lillehei, J. K. Longerbeam and J. C. Rosenberg. 1962. Shock: Its pathogenesis and treatment. Ciba Symposium. Springer-Verlag, Heidelberg.

Von Euler, U. S. 1964. Quantitation of stress by catecholamine analysis. Clinical Pharmacology Therapeutics 5: 398-404.

Weil, M. H. and A. A. Abdelmonen. 1970. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41: 989-1001.

Weil, M. H., L. D. MacLean, W. W. Spink and M. B. Visscher. 1956. Original not available; cited in R. C. Lillehei, J. K. Longerbeam and J. C. Rosenberg. 1962. Shock: Its pathogenesis and treatment. Ciba Symposium. Springer-Verlag, Heidelberg.

Weiss, G. M., D. G. Topel, D. G. Siers and J. H. Magilton. 1970. Relationships of plasma cortisol and growth hormone levels to muscle quality characteristics in normal and stress prone swine. Journal of Animal Science 31: 1018. (Abstr.)

Weiss, G. M., D. G. Topel, and R. C. Ewan. 1971. Growth comparison of a muscular and fat strain of swine II. Protein solubility characteristics and M. longissimus and serum electrolyte levels. Journal of Animal Science 32: 1124-1127.

Whelan, R. F. 1952. Vasodilation in human skeletal muscle during adrenaline infusions. Journal of Physiology 118: 575-587.

Whelan, R. F. 1954. The effects of adrenaline and noradrenaline on the blood flow through human muscle. Peripheral Circulation in Man. Ciba Foundation Symposium.

Whelan, R. F. and I. S. de la Lande. 1963. Action of adrenaline on limb blood vessels. British Medical Bulletin 19: 125-131.

Whipp, S. C. and N. Lyon. 1970. Hydrocortisone determination in bovine plasma. The Cornell Veterinarian 60: 582-587.

Whipp, S. C., R. L. Woodland and N. C. Lyon. 1970. Diurnal variation in concentrations of hydrocortisone in plasma of swine. American Journal of Veterinary Research 31: 2105-2107.

White, A., P. Handler, E. L. Smith and D. Stetten. 1968. Principles of biochemistry. McGraw-Hill Book Co., Inc., New York, New York.

Widdowson, E. M. and R. A. McCance. 1950. Chemical composition of newly born mammals. Nature 166: 626-635.

Widdowson, E. M. and R. A. McCance. 1956. The effect of development on the composition of the serum and extracellular fluids. Clinical Science 15: 361-369.

Wiggers, C. J. 1947. Original not available; cited in R. C. Lillehei, J. K. Longerbeam, J. H. Block and W. B. Manax. 1964. The modern treatment of shock based on physiologic principles. Clinical Pharmacology and Therapeutics 5: 63-101.

Wiggers, H. C., R. C. Ingraham, F. Roemhild and H. Goldgerg. 1948. Vasoconstriction and the development of irreversible hemorrhagic shock. American Journal of Physiology 153: 511-514.

Wiggers, C. J. and S. M. Werle. 1942. Cardiac and peripheral resistance factors as determinants of circulatory failure in hemorrhagic shock. American Journal of Physiology 136: 421-431.

Wilkins, H., N. Back, R. Steger and J. Karn. 1970. The influence of blood pH on peripheral vascular tone: Possible role of proteases and vasoactive polypeptides. In A. Bertelli and N. Back, eds. Shock--Biochemical, Pharmacological and Clinical Aspects. Pp. 201-214. Plenum Press, New York.

Wilson, R. F., A. D. Chiscans and E. Quadros. 1967. Some observations on 58 patients with cardiac shock. Anesthesia and Analgesia. Current Researches 46: 764-771.

Wilson, R. F., D. V. Jablonski and A. P. Thal. 1964. The usage of dibenzyline in clinical shock. Surgery 56: 172-181.

Wismer-Pedersen, J. 1959. Quality of pork in relation to rate of pH change post-mortem. Food Research 24: 711-717.

Wismer-Pedersen, J. and E. J. Briskey. 1961. Rate of anaerobic glycolysis vs. structure in pork muscle. Nature 189: 318-323.

Wolfson, S., R. A. Heinle, M. V. Herman, H. G. Kemp, J. M. Sullivan and R. Gorlin. 1966. Propranolol and angina pectores. American Journal of Cardiology 18: 345-352.

Wolfson, S. and R. Gorlin. 1969. Cardiovascular pharmacology of propranolol in man. Circulation 40: 501-511.

Wyman, L. C. and C. Tum Sudan. 1939. Original not available; cited in D. I. Shagal and G. L. Shraiberg. 1964. Adrenal cortex in myopathics, functional state. Federation Proceedings 23: 1253-1262.

Yamori, Y., W. Lovenberg and A. Sjoerdsma. 1970. Norepinephrine metabolism in brainstem of spontaneously hypertensive rats. Science 170: 544-546.

Youmans, W. B. 1967. The visceral nervous system and skeletal muscular activity. American Journal of Physical Medicine 46: 173-188.

Zsoter, T., L. Banderman and C. I. Chappel. 1961. The effect of "local" pH changes on blood flow in the dog. American Heart Journal 61: 777-782.

Zweifach, B. W. 1958. Original not available; cited in J. H. Block, C. J. Pierce and R. E. Lillehei. 1966. Adrenergic blocking agents in the treatment of shock. Annual Review of Medicine 17: 483-505.

Zweifach, B. W. 1961. Function of Microcirculation. Thomas, Springfield, Illinois.

Zweifach, B. W. 1968. Vasoactive agents in the microcirculation. Federation Proceedings 27: 1399-1402.

ACKNOWLEDGMENTS

The author wishes to express his gratitude and appreciation to his major research professor, Dr. David G. Topel, for his interest, thought, and research grant support during the four-year research effort conducted at Iowa State University in acquisition of the M.S. and Ph.D. degrees. In addition, the opportunity to coach three Intercollegiate Meat Judging teams and participate in undergraduate instruction under his guidance has been a very worthwhile experience during the author's advanced study.

The encouragement of the author's immediate family and friends is gratefully acknowledged. Sincere and humble gratitude is expressed to God for providing the determination and limited ability to fulfill the requirements of scholastic advancement.

The effort, advice, and working relationship of Dr. Richard C. Ewan will never be forgotten. The assistance of Dr. Gordon Thomson in analysis of the data is greatly appreciated. Appreciation is also expressed to Dr. Darrel E. Goll and Dr. David R. Griffith as instructors and members of the author's graduate committee. Dr. Lauren L. Christian and Dr. R. A. Ball will be remembered as members of the author's graduate committee and for their technical, scientific, and practical involvement in the author's graduate career.

The laboratory assistance of Dennis Walker, Dennis De Witt, and David Leonhart is appreciated. Sincere gratitude is expressed to T. Joseph Morrissey, ISU swine herdsman, for his effort and encouragement during the author's graduate career. And the highest respect is held for Donald G.

Wilson, first as a previous student and secondly as an invaluable assistant in conducting the technical research effort involved in this study.

APPENDIX

Figure 1. Fat strain Poland China and stress prone swine

a. Posterior view fat strain Poland China

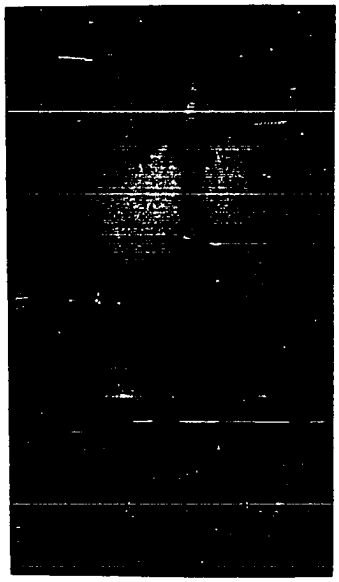
b. Dorsal view fat strain Poland China

c. Side view fat strain Poland China

d. Posterior view stress prone pig

e. Dorsal view stress prone pig

f. Side view stress prone pig



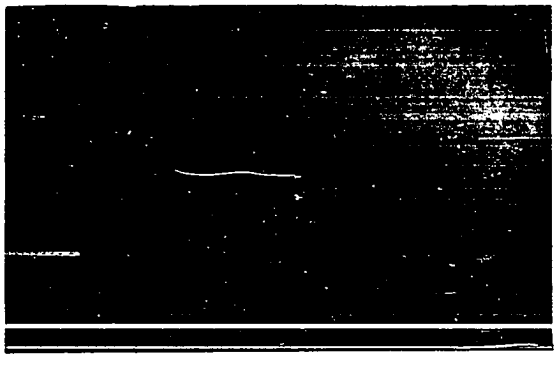


Figure 2. Catheterization

a. Restraint of tranquilized pig for catheterization

b. Position of needle and vinyl tubing for catheterization

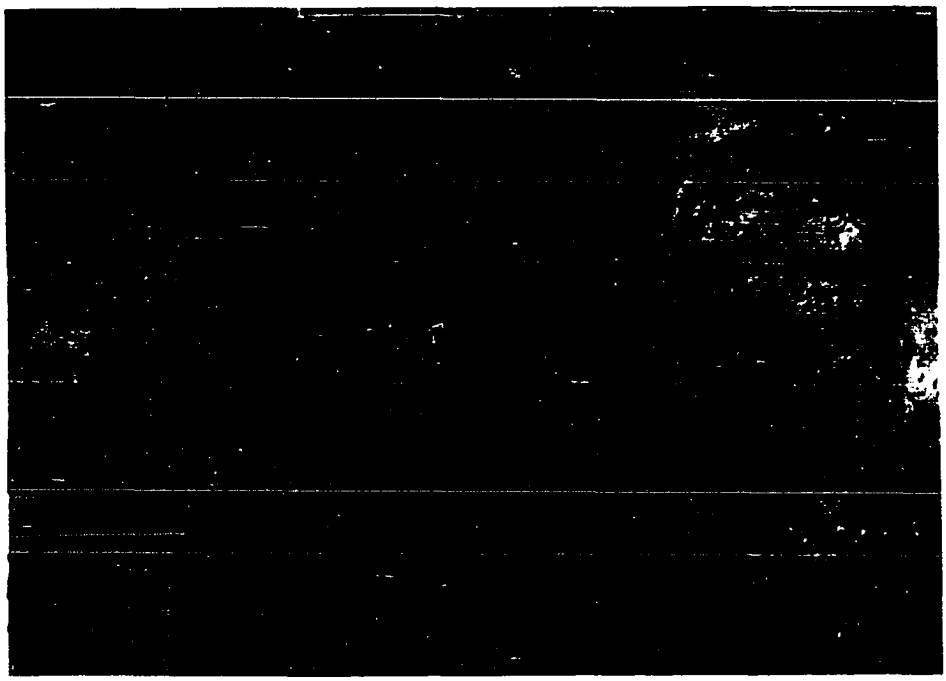
c. Needle removed, catheter imbedded within the venous circulation, and catheter tubing extending from cutaneous puncture laterally along the shoulder to the dorsal midline for termination between the two shoulders

d. Angle of needle with directionality toward the point of the opposite shoulder. Needle puncture approximately 1 cm away from the ventral midline

Figure 3. Microcirculatory hemorrhage of the rear leg musculature

a. Biceps femoris revealing microcirculatory hemorrhage

b. Cross section of rear leg musculature revealing microcirculatory hemorrhage



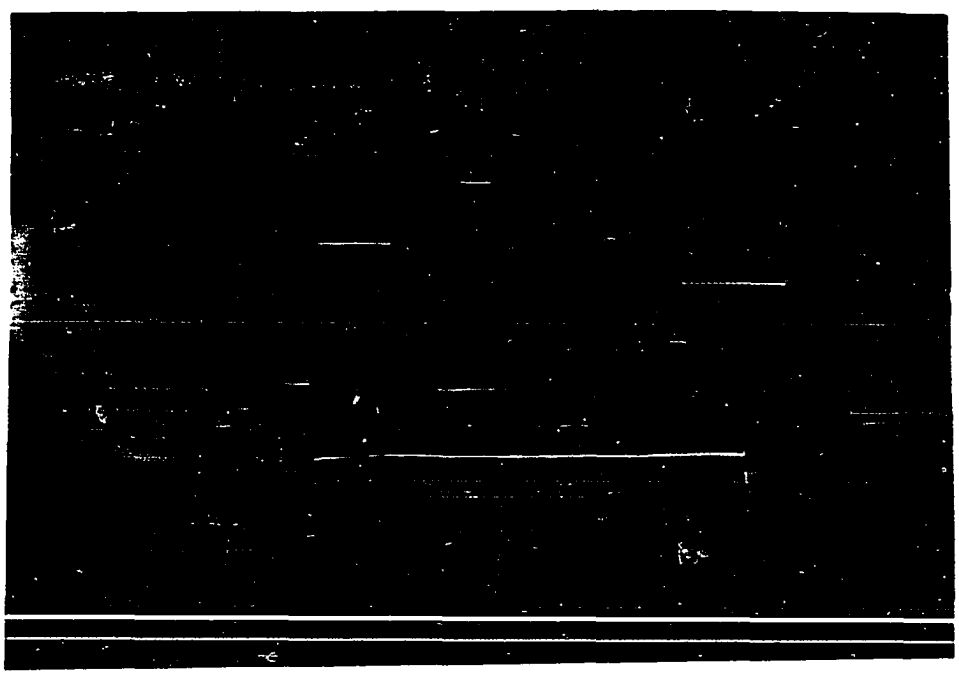


Figure 4. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma cortisol

Period 1.00 = A.M. plasma cortisol[a]
2.00 = P.M. plasma cortisol[a]
3.00 = basal non-stress A.M. plasma cortisol of control groups
4.00 = plasma cortisol after five minutes of physical stress within control groups of each strain[b]
5.00 = basal non-stress A.M. plasma cortisol for swine designated to receive phenoxybenzamine
6.00 = plasma cortisol after five minutes of physical stress within α adrenal blockade treated swine[b]
7.00 = basal non-stress A.M. plasma cortisol for swine designated to receive propranolol
8.00 = plasma cortisol after five minutes of physical stress within β adrenal blockade treated swine[b]

---

[a]Significant ($P < .05$) diurnal strain effect.

[b]Significant ($P < .01$) physical stress effect.

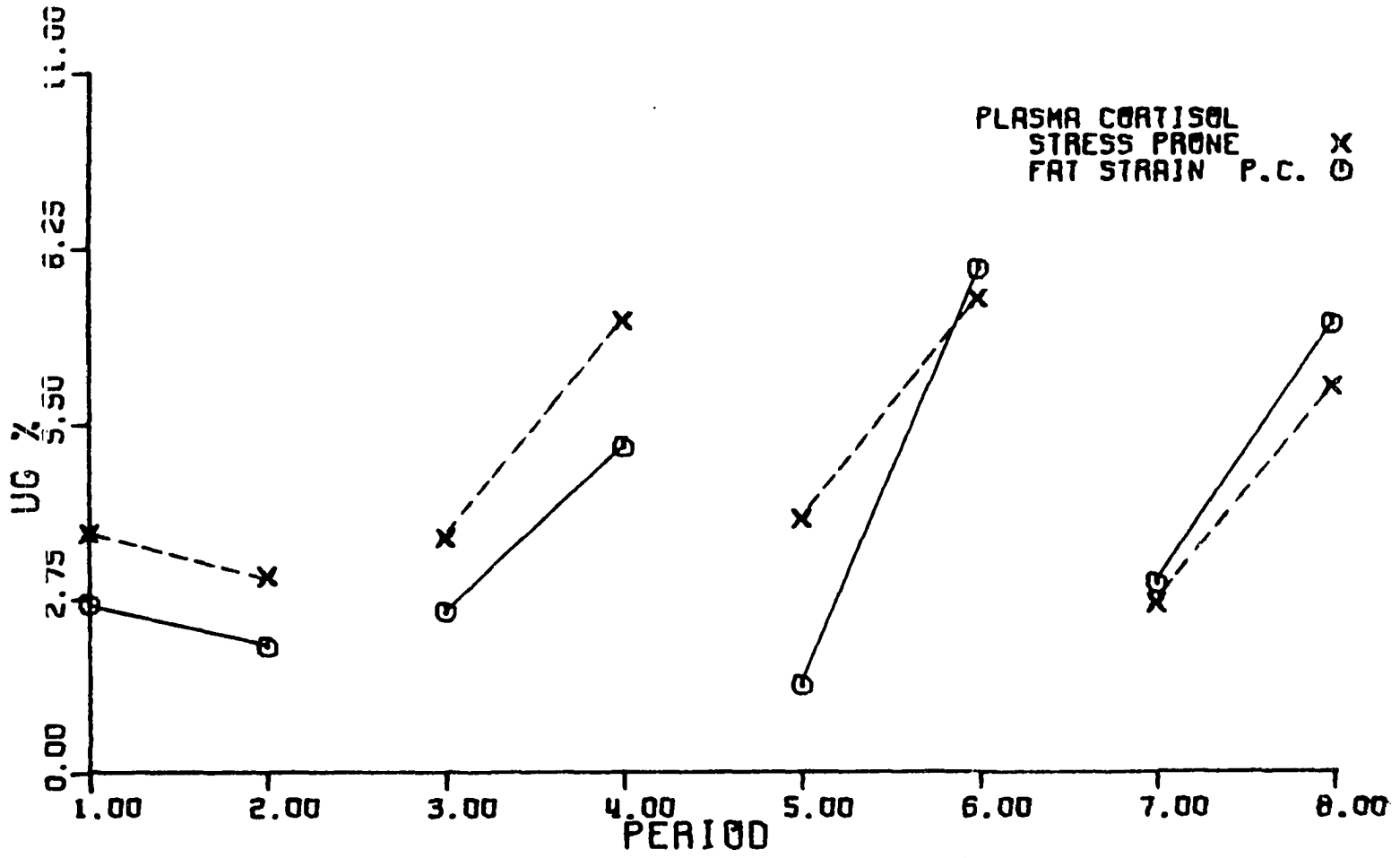

PLASMA CORTISOL
STRESS PRONE X
FAT STRAIN P.C. O
UG %
11.00
8.25
5.50
2.75
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 5. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma epinephrine

Period 1.00 = A.M. plasma epinephrine[a]
2.00 = P.M. plasma epinephrine[a]
3.00 = basal non-stress A.M. plasma epinephrine of control groups
4.00 = plasma epinephrine after five minutes of physical stress within control groups of each strain[b]
5.00 = basal non-stress A.M. plasma epinephrine for swine designated to receive phenoxybenzamine
6.00 = plasma epinephrine after five minutes of physical stress within α adrenal blockade treated swine[b]
7.00 = basal non-stress A.M. plasma epinephrine for swine designated to receive propranolol
8.00 = plasma epinephrine after five minutes of physical stress within β adrenal blockade treated swine[b]

---

[a]Significant ($P < .05$) diurnal strain effect.

[b]Significant ($P < .01$) physical stress effect.

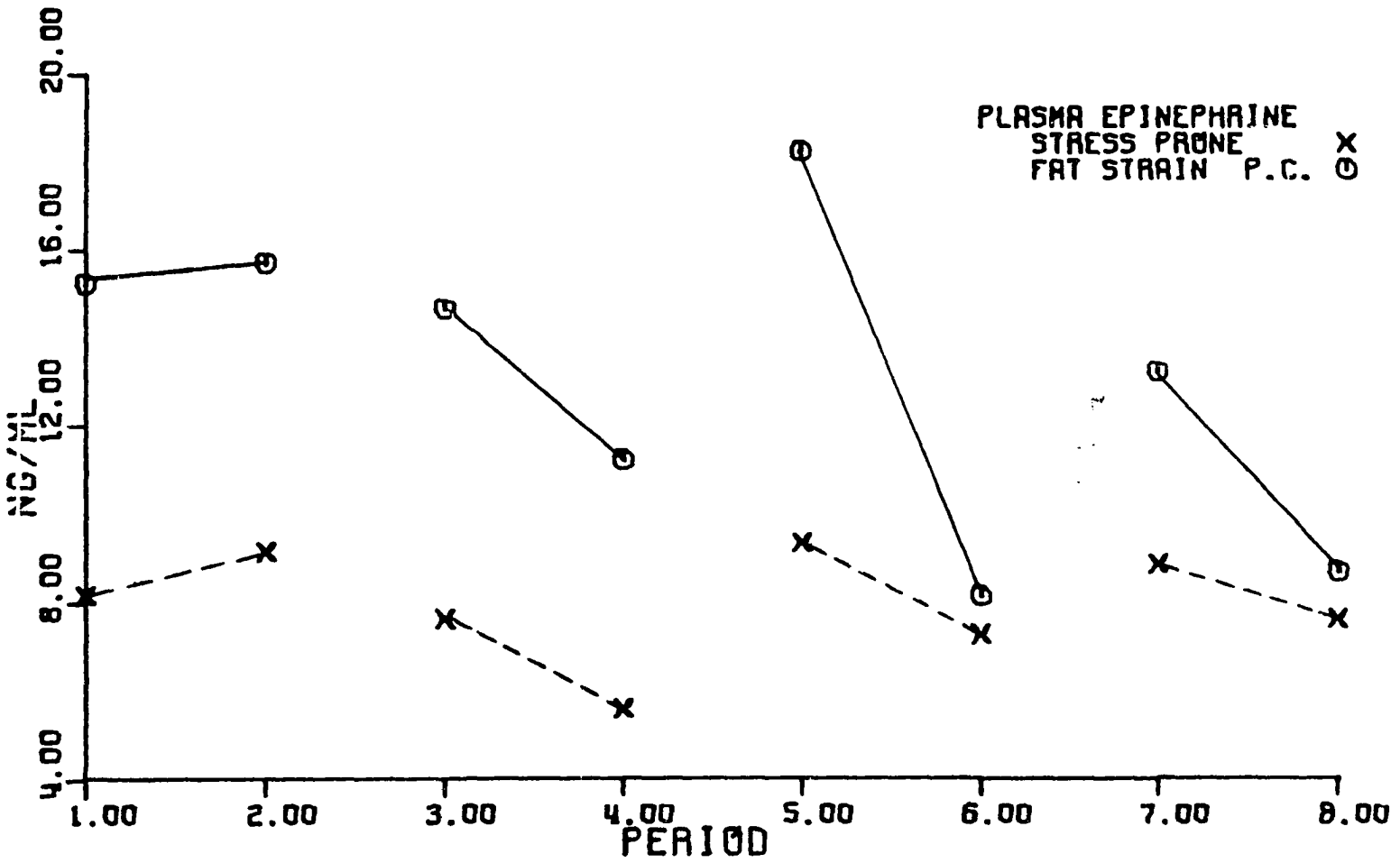

PLASMA EPINEPHRINE
STRESS PRONE X
FAT STRAIN P.C. O
NG/ML
20.00
16.00
12.00
8.00
4.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 6. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma glucose

Period 1.00 = A.M. plasma glucose[a]
2.00 = P.M. plasma glucose[a]
3.00 = basal non-stress A.M. plasma glucose of control groups
4.00 = plasma glucose after five minutes of physical stress within control groups of each strain[b]
5.00 = basal non-stress A.M. plasma glucose for swine designated to receive phenoxybenzamine
6.00 = plasma glucose after five minutes of physical stress within α adrenal blockade treated swine[b]
7.00 = basal non-stress A.M. plasma glucose for swine designated to receive propranolol
8.00 = plasma glucose after five minutes of physical stress within β adrenal blockade treated swine[b]

---

[a]Significant ($P < .01$) diurnal strain effect.

[b]Significant ($P < .01$) physical stress effect.

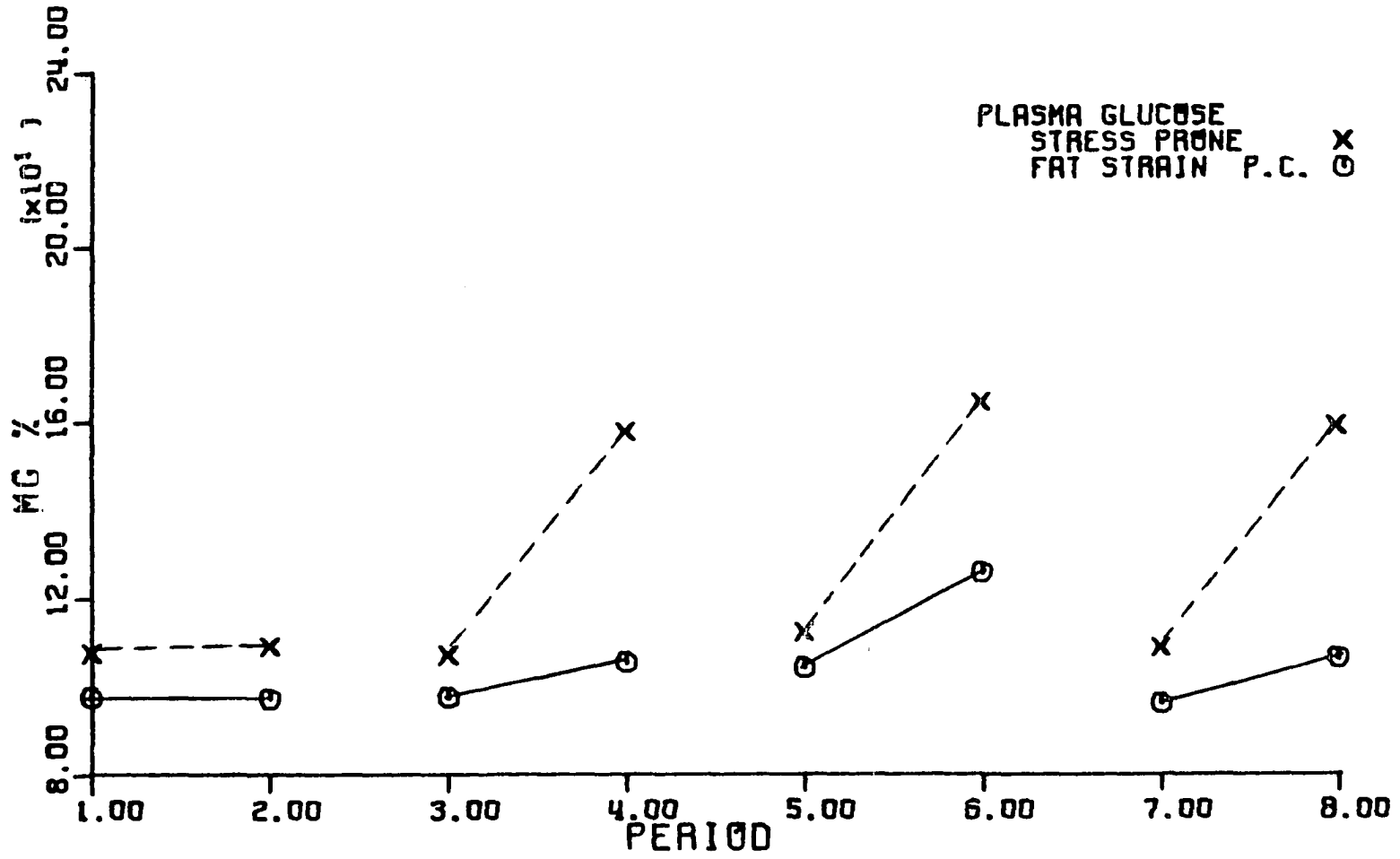

PLASMA GLUCOSE
STRESS PRONE X
FAT STRAIN P.C. ⊙
MG %
(x10¹)
24.00
20.00
16.00
12.00
8.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 7. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma lactate

Period 1.00 = A.M. plasma lactate
2.00 = P.M. plasma lactate
3.00 = basal non-stress A.M. plasma lactate of control groups
4.00 = plasma lactate after five minutes of physical stress within control groups of each strain[a,b,c]
5.00 = basal non-stress A.M. plasma lactate for swine designated to receive phenoxybenzamine
6.00 = plasma lactate after five minutes of physical stress within α adrenal blockade treated swine[a,b,c]
7.00 = basal non-stress A.M. plasma lactate for swine designated to receive propranolol
8.00 = plasma lactate after five minutes of physical stress within β adrenal blockade treated swine[a,b,c]

---

[a]Significant ($P < .01$) physical stress effect.

[b]Significant ($P < .05$) physical stress effect for fat strain P.C.

[c]Significant ($P < .01$) physical stress effect for stress prone swine.

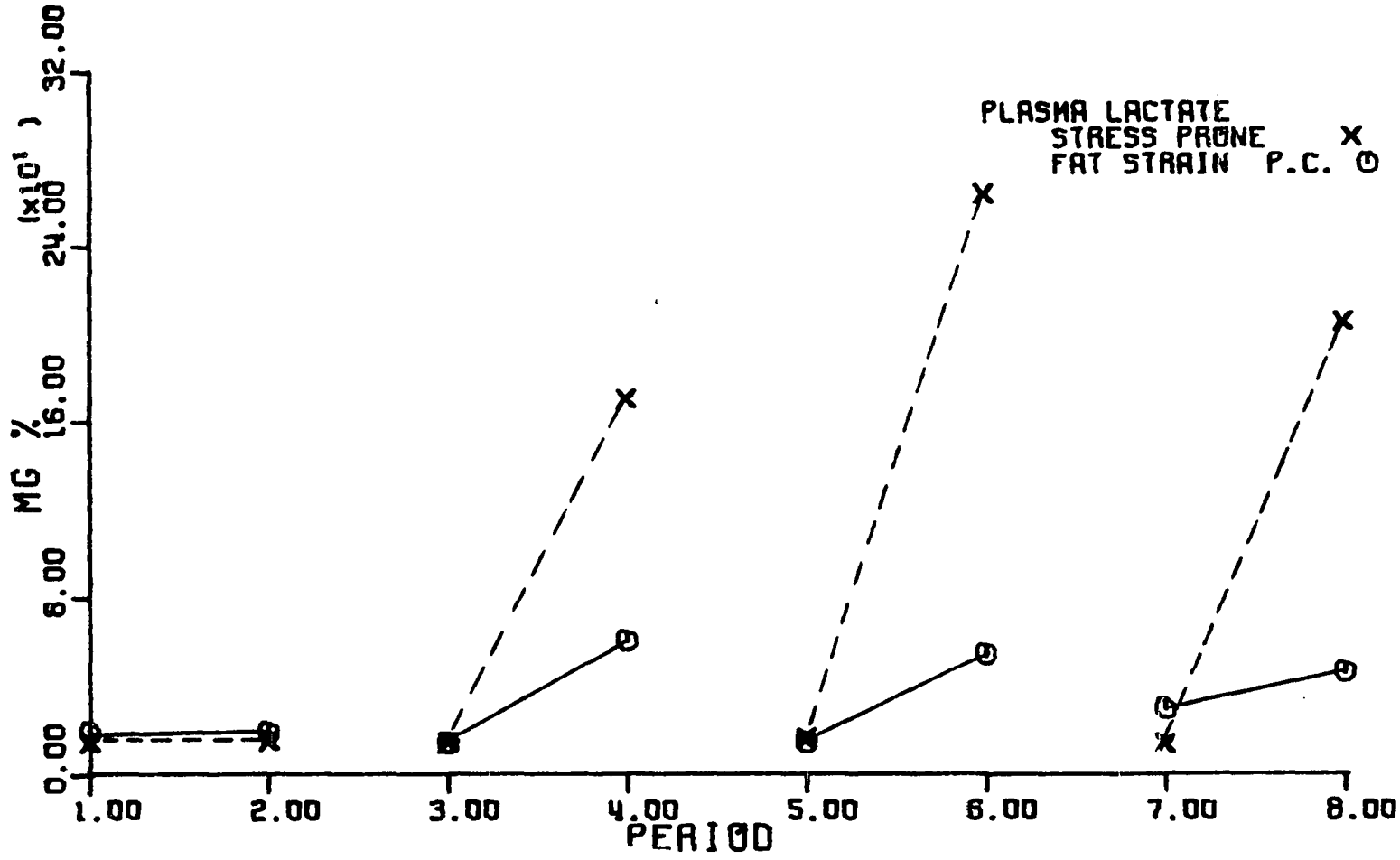

PLASMA LACTATE
STRESS PRONE X
FAT STRAIN P.C. ⊙
MG %
(x10¹)
0.00
8.00
16.00
24.00
32.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 8. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for blood pH

Period 1.00 = A.M. blood pH[a]
2.00 = P.M. blood pH[a]
3.00 = basal non-stress A.M. blood pH of control groups
4.00 = blood pH after five minutes of physical stress within control groups of each strain
5.00 = basal non-stress A.M. blood pH for swine designated to receive phenoxybenzamine
6.00 = blood pH after five minutes of physical stress within α adrenal blockade treated swine[b]
7.00 = basal non-stress A.M. blood pH for swine designated to receive propranolol
8.00 = blood pH after five minutes of physical stress within β adrenal blockade treated swine[b]

---

[a]Significant ($P < .01$) diurnal effect.

[b]Significant ($P < .01$) physical stress effect for stress prone strain.

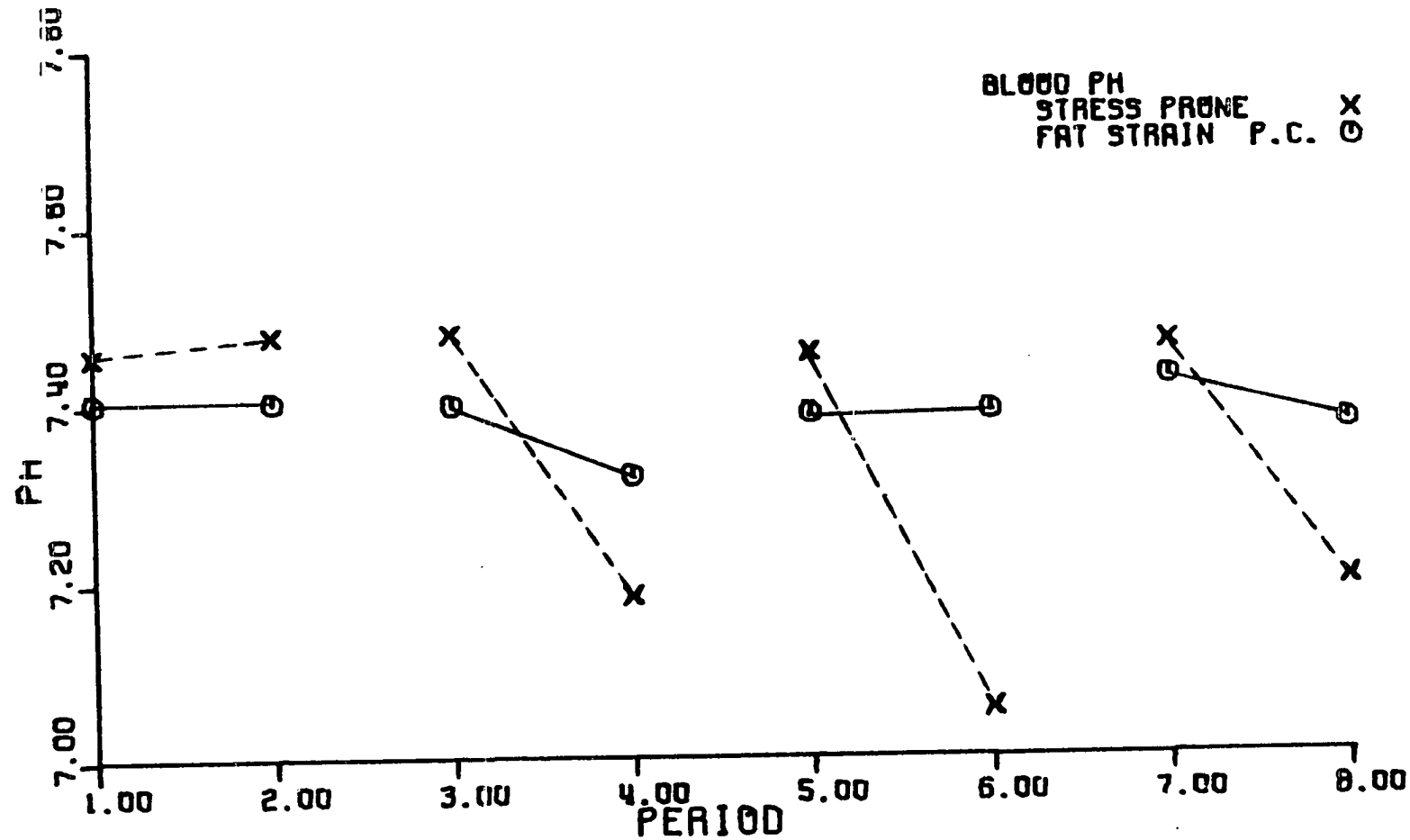

BLOOD PH
STRESS PRONE X
FAT STRAIN P.C. O
7.60
7.80
7.40
7.20
7.00
PH
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 9. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma sodium

Period 1.00 = A.M. plasma sodium
2.00 = P.M. plasma sodium
3.00 = basal non-stress A.M. plasma sodium of control groups
4.00 = plasma sodium after five minutes of physical stress within control groups of each strain
5.00 = basal non-stress A.M. plasma sodium for swine designated to receive phenoxybenzamine
6.00 = plasma sodium after five minutes of physical stress within α adrenal blockade treated swine
7.00 = basal non-stress A.M. plasma sodium for swine designated to receive propranolol
8.00 = plasma sodium after five minutes of physical stress within β adrenal blockade treated swine

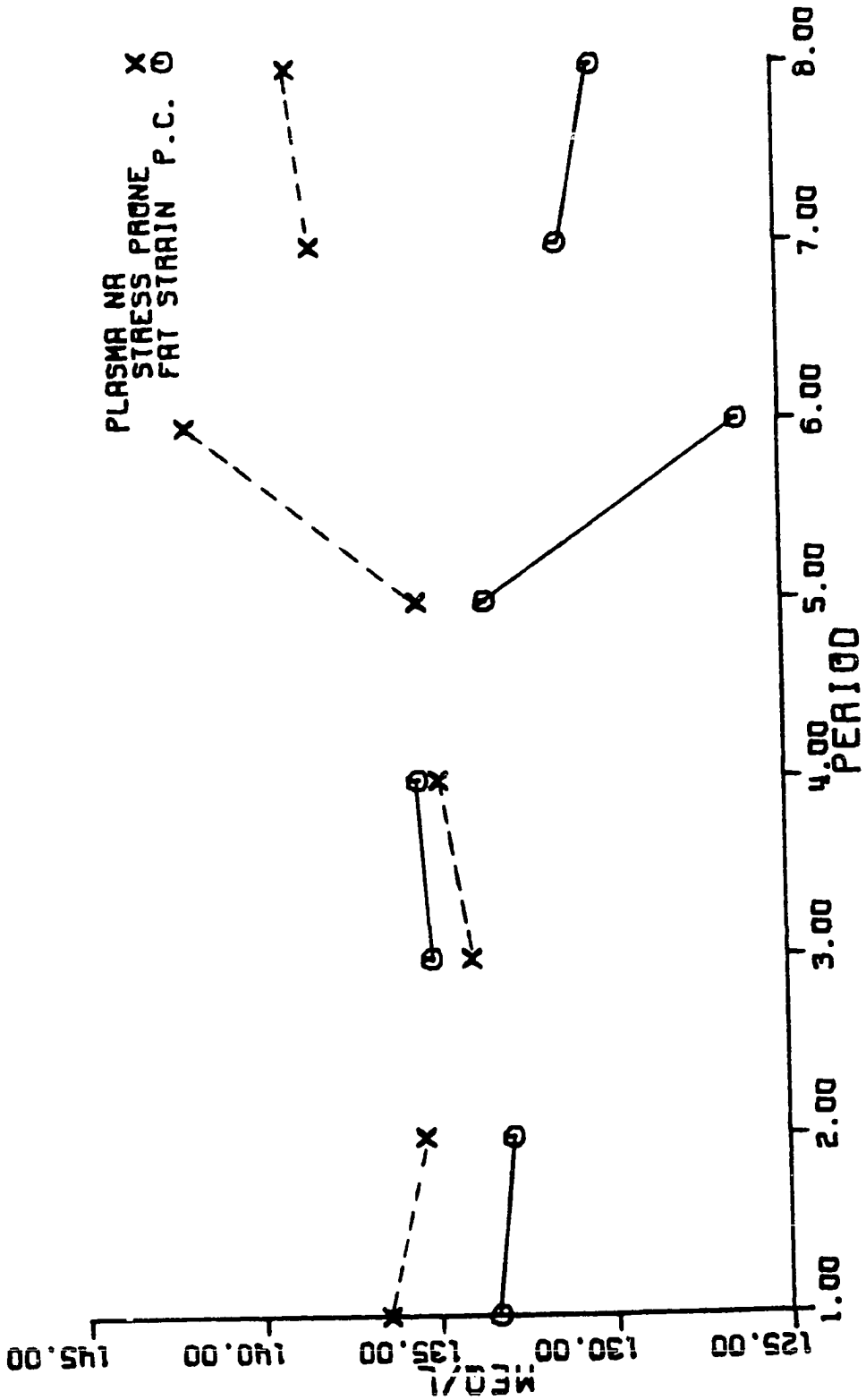

PLASMA NA
STRESS PRONE
FAT STRAIN P.C.
MEQ/L
125.00
130.00
135.00
140.00
145.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 10. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma potassium

Period 1.00 = A.M. plasma potassium[a]
2.00 = P.M. plasma potassium[a]
3.00 = basal non-stress A.M. plasma potassium of control groups
4.00 = plasma potassium after five minutes of physical stress within control groups of each strain
5.00 = basal non-stress A.M. plasma potassium for swine designated to receive phenoxybenzamine
6.00 = plasma potassium after five minutes of physical stress within α adrenal blockade treated swine
7.00 = basal non-stress A.M. plasma potassium for swine designated to receive propranolol
8.00 = plasma potassium after five minutes of physical stress within β adrenal blockade treated swine

---

[a]Significant ($P < .01$) diurnal strain effect.

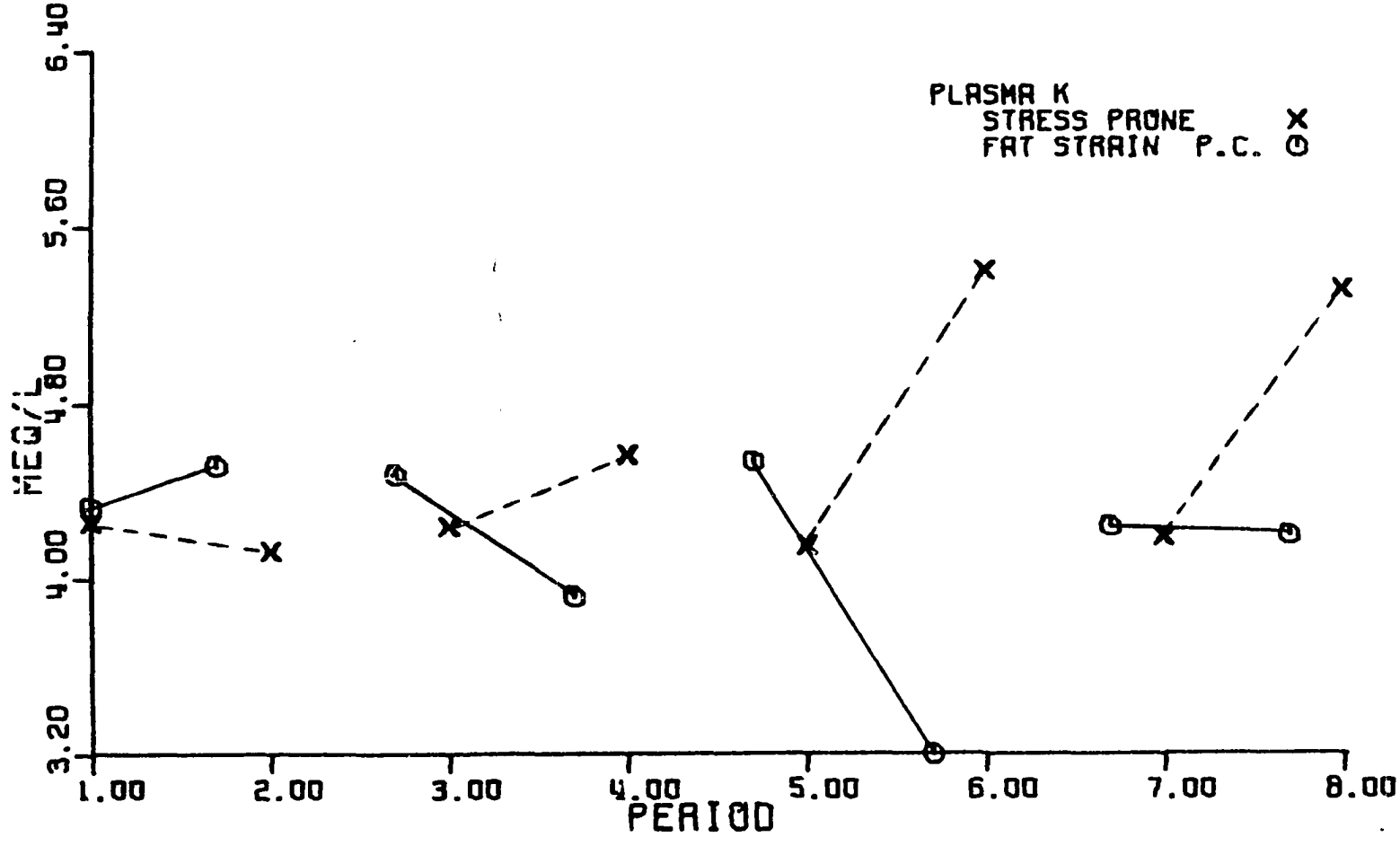

PLASMA K
STRESS PRONE X
FAT STRAIN P.C. ⊖
MEQ/L
6.40
5.60
4.80
4.00
3.20
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 11. Diurnal basal non-stress, basal A.M., and stress response as influenced by adrenergic blockade for plasma chloride

Period 1.00 = A.M. plasma chloride
2.00 = P.M. plasma chloride
3.00 = basal non-stress A.M. plasma chloride of control groups
4.00 = plasma chloride after five minutes of physical stress within control groups of each strain
5.00 = basal non-stress A.M. plasma chloride for swine designated to receive phenoxybenzamine
6.00 = plasma chloride after five minutes of physical stress within α adrenal blockade treated swine
7.00 = basal non-stress A.M. plasma chloride for swine designated to receive propranolol
8.00 = plasma chloride after five minutes of physical stress within β adrenal blockade treated swine

---

[a]Significant ($P < .01$) diurnal strain effect.

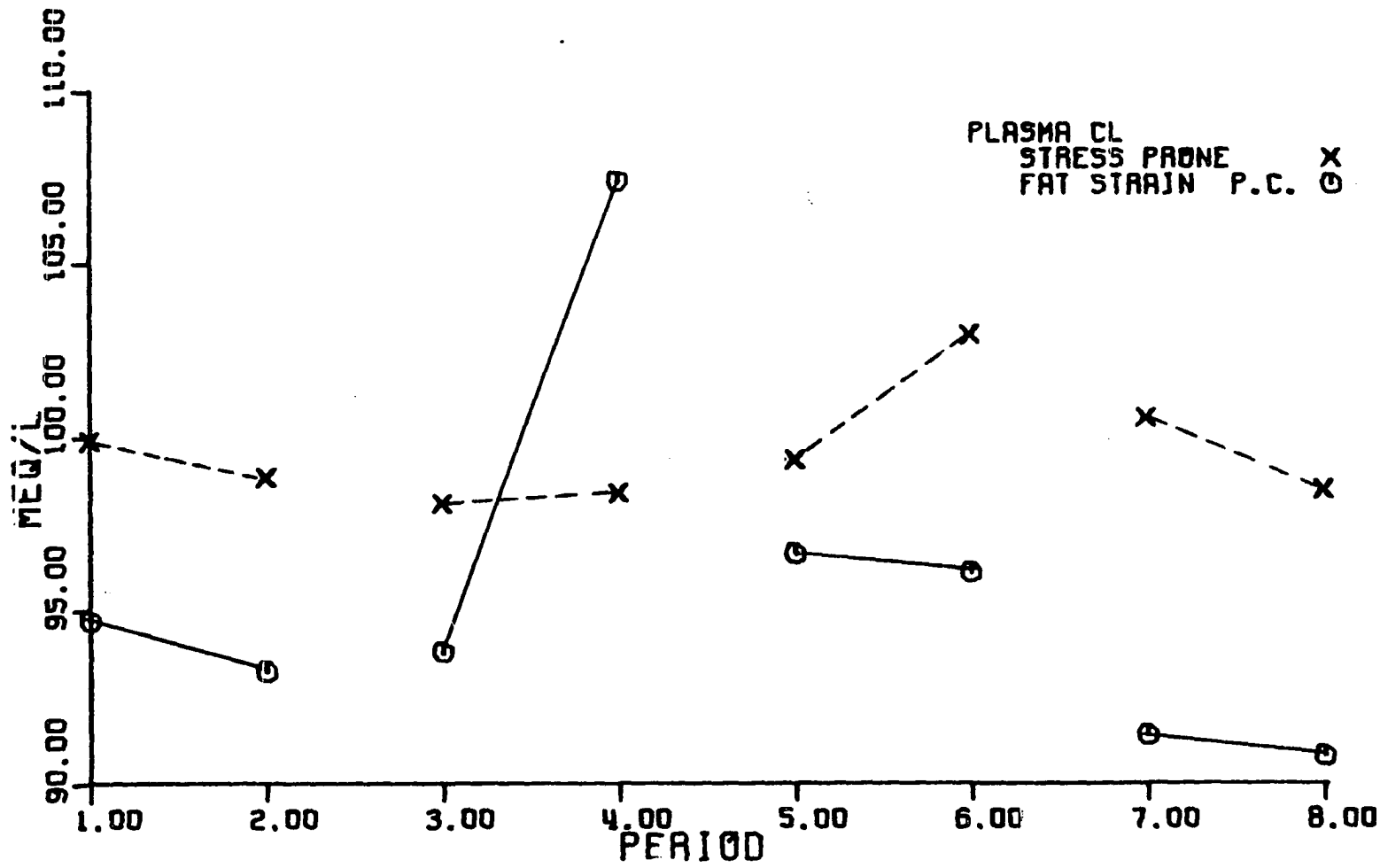
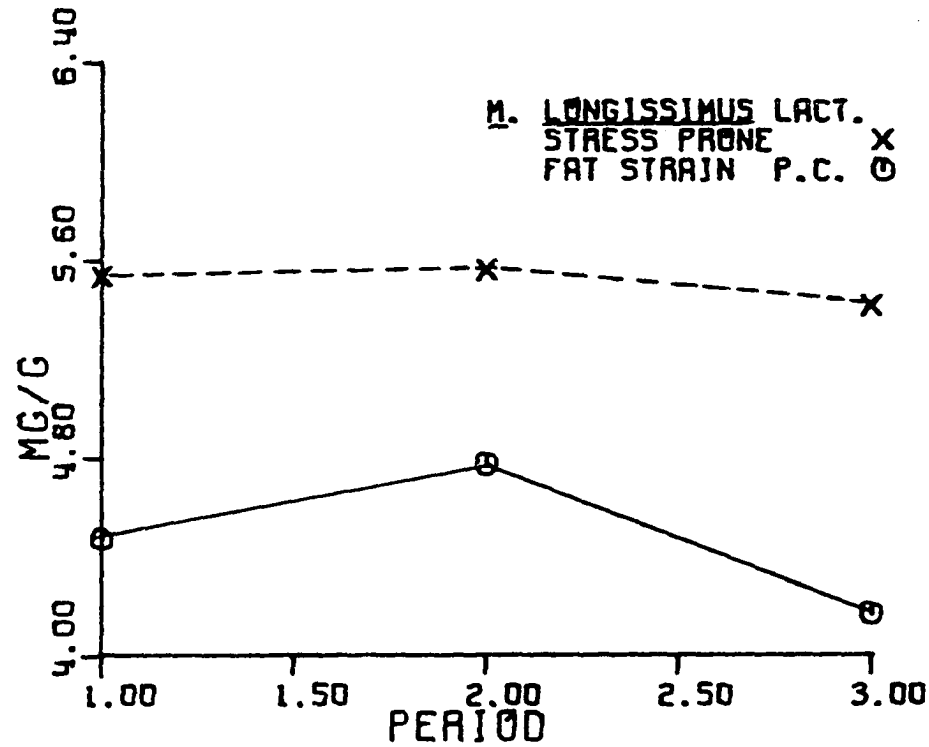

PLASMA CL
STRESS PRONE X
FAT STRAIN P.C. O
MEQ/L
110.00
105.00
100.00
95.00
90.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
PERIOD

Figure 12. Composite zero, three, and 24 hour post-mortem M. longissimus lactate

Period 1.00 = control swine
2.00 = α adrenergic blockade swine
3.00 = β adrenergic blockade swine

Figure 13. Composite zero, three, and 24 hour post-mortem M. longissimus pH

Period 1.00 = control swine
2.00 = α adrenergic blockade swine
3.00 = β adrenergic blockade swine


M. LONGISSIMUS LACT.
STRESS PRONE X
FAT STRAIN P.C. O
MG/G
6.40
5.60
4.80
4.00
1.00
1.50
2.00
2.50
3.00
PERIOD

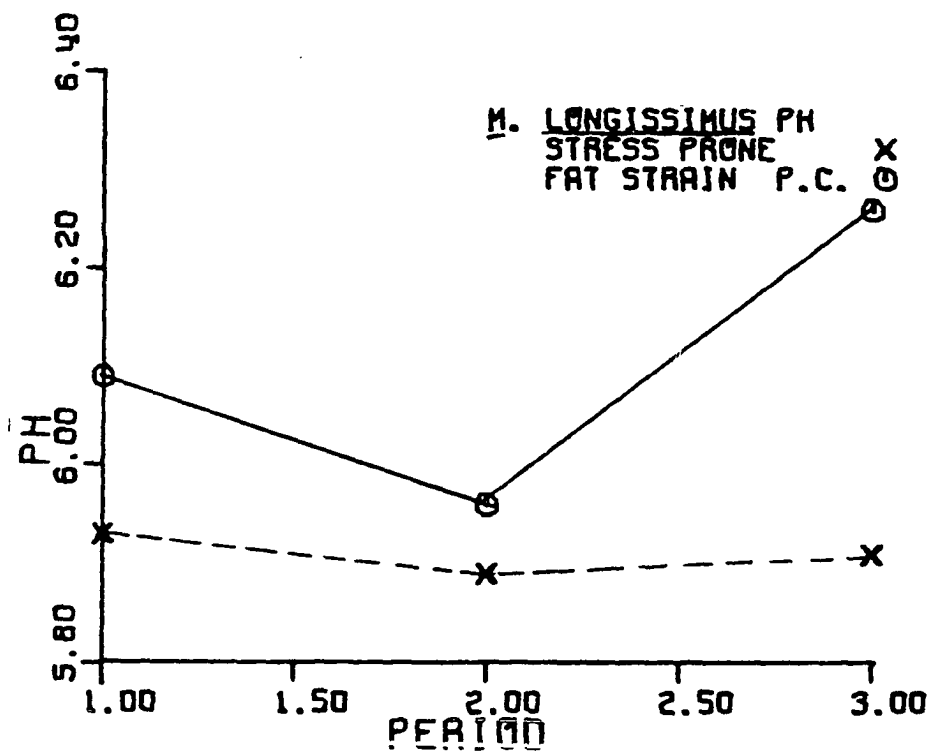

M. LONGISSIMUS PH
STRESS PRONE X
FAT STRAIN P.C. O
PH
6.40
6.20
6.00
5.80
1.00
1.50
2.00
2.50
3.00
PERIOD

Figure 14. Composite zero, three, and 24 hour post-mortem M. longissimus color

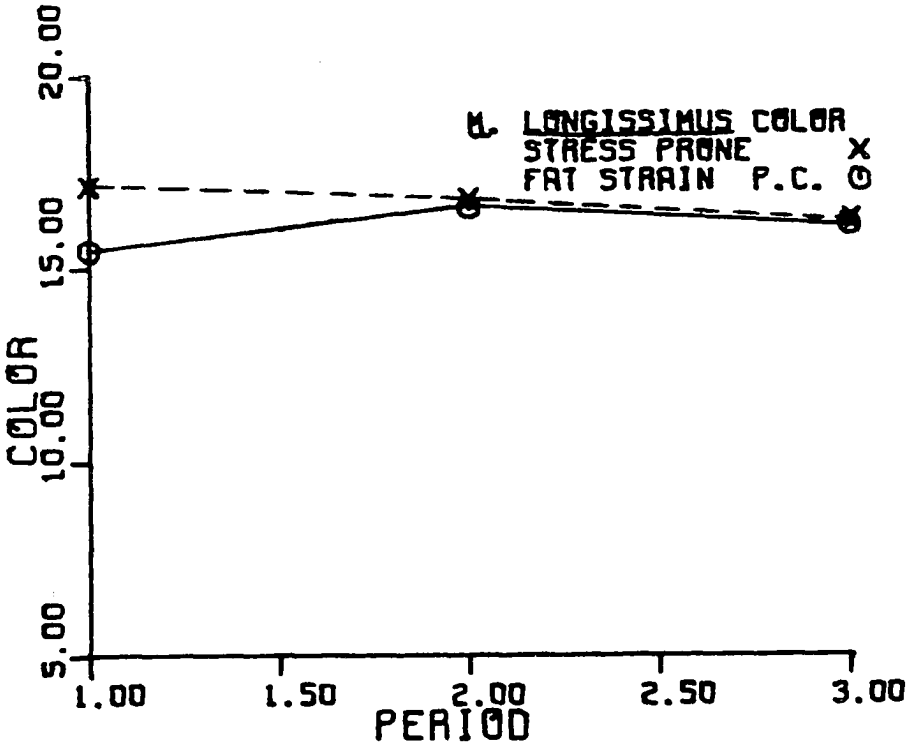
Period 1.00 = control swine
2.00 = α adrenergic blockade swine
3.00 = β adrenergic blockade swine

Figure 15. Ten minute post-mortem liver lactate[a]

Period 1.00 = control swine
2.00 = α adrenergic blockade swine
3.00 = β adrenergic blockade swine

---

[a]Significant ($P < .05$) strain effect.


L. LONGISSIMUS COLOR
STRESS PRONE X
FAT STRAIN P.C. O
COLOR
20.00
15.00
10.00
5.00
1.00
1.50
2.00
2.50
3.00
PERIOD

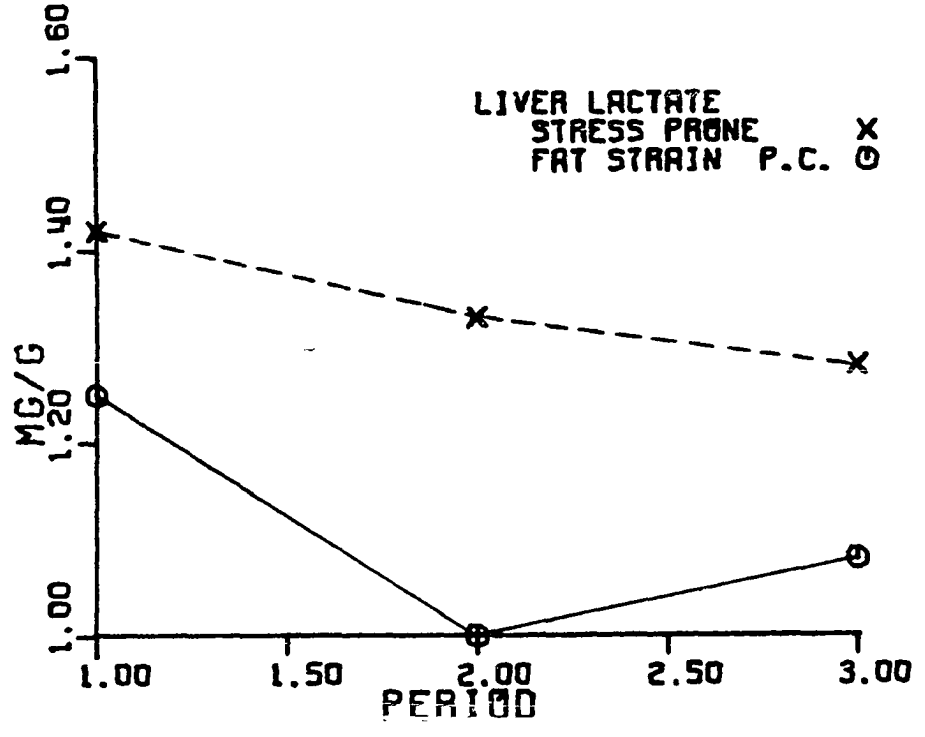

LIVER LACTATE
STRESS PRONE X
FAT STRAIN P.C. O
MG/G
1.60
1.40
1.20
1.00
1.00
1.50
2.00
2.50
3.00
PERIOD

Table 16. Selected least squares analysis of variance table presenting mean squares for plasma cortisol, plasma epinephrine, plasma lactate, and blood pH

Source	d.f.	Cortisol	d.f.	Epinephrine	d.f.	Lactate	d.f.	pH
Total	142		135		139		132	
Total reduction	7	185.27	7	3109.06	7	6342.23	7	1042.68
Correction term	1	1191.74	1	19400.16	1	40898.46	1	7235.44
Group	1	47.24*	1	1544.68**	1	742.43	1	0.13**
Treatment	2	2.27	2	109.04	2	712.36	2	0.01
Group x treatment	2	25.18	2	60.48	2	1025.21	2	0.01
Animals	30	9.09**	30	35.01**	30	288.92	30	0.00
Time	1	0.86	1	0.83	1	8.47	1	0.00
Remainder	105	2.43	98	14.57	102	138.46	95	0.00

*Significant ($P < .05$).

**Significant ($P < .01$).

Table 17. Selected least squares analysis of variance table presenting mean squares for plasma glucose, plasma sodium, plasma potassium, and plasma chloride

Source	d.f.	Glucose	d.f.	Sodium	d.f.	Potassium	d.f.	Chloride
Total	142		140		139		140	
Total reduction	7	437846.44	7	362480.30	7	368.64	7	187019.61
Correction term	1	2458963.70	1	2534224.74	1	2577.83	1	1306584.10
Group	1	70776.15**	1	238.49	1	1.77	1	1006.77
Treatment	2	99467.82**	2	1.23	2	0.28	2	64.41
Group x treatment	2	101513.31**	2	199.57	2	0.32	2	132.50
Animals	30	3197.70**	30	245.04**	30	0.20	30	29.87
Time	1	129455.91**	1	35.51	1	0.07	1	13.52
Remainder	105	21524.17	103	56.22	102	0.14	103	23.55

**Significant ($P < .01$).

Table 18. Selected least squares analysis of variance table presenting mean squares for stressed plasma cortisol, stressed plasma epinephrine, stressed plasma lactate, and stressed blood pH

Source	d.f.	Stressed plasma cortisol	d.f.	Stressed plasma epinephrine	d.f.	Stressed plasma lactate	d.f.	Stressed blood pH
Total	36		33		34		36	
Total reduction	6	286.45	6	376.57	6	18326.08	6	315.51
Correction term	1	1687.02	1	2156.08	1	982642.68	1	1892.52
Group	1	0.27	1	52.23*	1	30116.23**	1	0.45**
Treatment	2	8.07	2	1.37	2	989.86	2	0.01
Group x treatment	2	7.65	2	19.05	2	207.29	2	0.03
Remainder	30	11.68	27	7.39	28	920.58	30	0.01

*Significant ($P < .05$).

**Significant ($P < .01$).

Table 19. Selected least squares analysis of variance table presenting mean squares for stressed plasma glucose, stressed plasma sodium, stressed plasma potassium, and stressed plasma chloride

Source	d.f.	Stressed plasma glucose	d.f.	Stressed plasma sodium	d.f.	Stressed plasma potassium	d.f.	Stressed plasma chloride
Total	35		35		34		34	
Total reduction	6	113152.02	6	106170.89	6	118.26	6	55919.87
Correction term	1	650630.32	1	630938.82	1	652.89	1	325859.28
Group	1	20034.59**	1	547.55*	1	14.93**	1	28.09
Treatment	2	663.51	2	3.44	2	0.96	2	205.64
Group x treatment	2	177.16	2	193.22	2	1.77	2	258.53
Remainder	29	601.47	29	99.13	28	0.62	28	121.26

*Significant ($P < .05$).

**Significant ($P < .01$).

Table 20. Selected least squares analysis of variance table presenting mean squares for M. longissimus lactate, M. longissimus pH, M. longissimus color, and liver lactate

Source	d.f.	M. longissimus lactate	d.f.	M. longissimus pH	d.f.	M. longissimus color	Source	d.f.	Liver lactate
Total	108		108		108		Total	36	
Total reduction	8	370.18	8	489.26	8	3787.57	Total reduction	6	9.17
Correction term	1	2687.02	1	3894.84	1	29087.05	Correction term	1	54.27
Group	1	28.73**	1	1.03	1	13.51	Group	1	0.49*
Treatment	2	1.27	2	0.23	2	2.38	Treatment	2	0.10
Group x treatment	2	0.51	2	0.18	2	6.73	Group x treatment	2	0.02
Animals	30	1.38*	30	0.61**	30	7.67	Remainder	30	0.08
Time	2	121.06**	2	8.67**	2	590.89**			
Remainder	70	0.84	70	0.04	70	5.65			

*Significant ($P < .05$).

**Significant ($P < .01$).

Table 21. Correlation coefficients between 0, 3, and 24 hour post-mortem M. longissimus lactate and stress pH, epinephrine, cortisol, glucose, lactate, and potassium

		Stress prone	Fat strain P.C.
0 hr. lactate vs.	after stress blood pH	-0.215	-0.231
	after stress epinephrine	0.019	-0.090
	after stress cortisol	0.392	0.417
	after stress glucose	0.119	0.418
	after stress lactate	0.234	0.045
	after stress potassium	0.144	-0.486*
3 hr. lactate vs.	after stress blood pH	-0.336	-0.388
	after stress epinephrine	0.050	-0.018
	after stress cortisol	0.383	0.332
	after stress glucose	0.407	0.451
	after stress lactate	0.362	0.178
	after stress potassium	0.420	-0.486
24 hr. lactate vs.	after stress blood pH	0.025	0.359
	after stress epinephrine	-0.138	0.344
	after stress cortisol	0.041	0.311
	after stress glucose	0.284	-0.351
	after stress lactate	-0.062	-0.393
	after stress potassium	0.245	-0.003

*Significant ($P < .05$).

Table 22. Correlation coefficients between 0, 3, and 24 hour post-mortem *M. longissimus* pH and stress pH, epinephrine, cortisol, glucose, lactate, and potassium

		Stress prone	Fat strain P.C.
0 hr. pH vs.	after stress blood pH	0.292	0.357
	after stress epinephrine	-0.096	0.064
	after stress cortisol	-0.095	-0.237
	after stress glucose	-0.326	-0.488*
	after stress lactate	-0.244	-0.464
	after stress potassium	-0.247	0.584*
3 hr. pH vs.	after stress blood pH	0.203	0.250
	after stress epinephrine	-0.395	-0.062
	after stress cortisol	-0.354	-0.454
	after stress glucose	-0.381	-0.493*
	after stress lactate	-0.297	-0.279
	after stress potassium	-0.362	0.519*
24 hr. pH vs.	after stress blood pH	0.269	-0.461
	after stress epinephrine	0.305	-0.149
	after stress cortisol	-0.166	0.276
	after stress glucose	-0.387	0.025
	after stress lactate	-0.020	-0.099
	after stress potassium	-0.344	0.309

*Significant ($P < .05$).

Table 23. Correlation coefficients between 0, 3, and 24 hour post-mortem *M. longissimus* color and stress pH, epinephrine, cortisol, glucose, lactate, and potassium

		Stress prone	Fat strain P.C.
0 hr. color vs.	after stress blood pH	-0.007	-0.138
	after stress epinephrine	0.220	-0.344
	after stress cortisol	0.260	-0.116
	after stress glucose	0.266	-0.389
	after stress lactate	0.112	-0.697**
	after stress potassium	0.004	0.353
3 hr. color vs.	after stress blood pH	-0.575*	-0.071
	after stress epinephrine	-0.150	-0.155
	after stress cortisol	0.291	0.420
	after stress glucose	0.471*	-0.407
	after stress lactate	0.490*	0.076
	after stress potassium	0.522*	-0.200
24 hr. color vs.	after stress blood pH	-0.354	-0.074
	after stress epinephrine	-0.036	-0.203
	after stress cortisol	0.434	-0.416
	after stress glucose	0.507*	0.019
	after stress lactate	0.216	-0.098
	after stress potassium	0.568*	0.068

*Significant ($P < .05$).

**Significant ($P < .01$).