Heat

MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

May 25, 1972

TABLE OF CONTENTS

INTRODUCTION

Of the few truly acute medical emergencies such as shock, coma, bleeding, airway obstruction, pulmonary edema, cardiac arrhythmia or poisoning, none is more emergent in nature than heat stroke. Since summer is nearly upon us again, heat stroke and its related conditions seems worthy of discussion.

My intention on this occasion is four-fold. First, to briefly summarize important aspects of an overwhelming literature on physiologic mechanisms and responses which occur as an individual gains tolerance to work in the heat; second, to review the three main disorders associated with environmental heat stress, namely heat cramp, heat exhaustion, and heat stroke; third, to enumerate certain recently described factors which appear to be important in the pathogenesis of heat stroke; and fourth, to stress the often devastating type of heat stroke which afflicts otherwise healthy young men as a result of extraordinary physical exertion.

Physiological events during hard work in a hot environment.

Acclimatization to heat is a physiologic process by which an individual becomes able to tolerate work in a hot environment. When considering acclimatization, one must always qualify the term to indicate "acclimatization to what". Obviously, sufficient acclimatization may be attained to permit a secretary to stand quite comfortably on a street corner at high noon in August while waiting for a bus without danger of collapse from the heat. But such acclimatization is by no means comparable to that required of a man who can tolerate eight to ten hours of hard physical labor in the hot sun.

Table I lists certain physiological consequences of hard work in the heat.

PHYSIOLOGIC EVENTS DURING HARD PHYSICAL WORK
IN A HOT ENVIRONMENT

I. FEVER

- A. Exogenous
- B. Endogenous

II. CARDIOVASCULAR RESPONSE

- A. Peripheral Circulatory Changes
  1. Massive shunt to skeletal muscle
     - a. blood flow increases (active hyperemia)
     - b. osmotic movement of plasma water to skeletal muscle cells
  2. Cutaneous vasodilatation
  3. Splanchnic vasoconstriction

PHYSIOLOGIC EVENTS DURING HARD PHYSICAL WORK
IN A HOT ENVIRONMENT

II. (continued)

4. Sweating

INCREASED VASCULAR CAPACITY MUSCLE/SKIN PLUS
VOLUME OF SWEAT LOST EXCEEDS VOLUME GAINED
BY SPLANCHNIC VASO-
CONSTRICTION

NET EFFECT: DECREASED ARTERIAL VOLUME

B. Central Circulatory Response to Decreased Arterial Volume
   1. Venous return falls
   2. Stroke volume falls
   3. Heart rate increases
   4. Cardiac output maintained, rises or may fall

III. MAJOR ENDOCRINE RESPONSES TO HEAT STRESS

A. Activation of Renin - Angiotensin System
B. Aldosterone Production Increases
C. Growth Hormone Released
D. Cortisol

IV. RENAL RESPONSE

A. GFR/RPF Fall
B. Na+ Conservation
C. Oliguria

Fever is invariable. It occurs by heat gain from two major sources. The first, exogenous, is that derived from heated air or the sun. By this means, heat is transferred by electromagnetic waves (radiation) or by diffusion and convection from air if the air is hotter than the body surface. An individual exposed to the bright sun will gain an average of 150 kcal/hour.

Endogenous heat is derived from metabolic processes and these in turn vary with physical activity. Basal heat production averages 65 to 85 kcal/hour. During moderate work, metabolic heat will average about 300 kcal/hour; maximal work may generate from 600 and for only brief periods, up to 900 kcal/hour. (1)

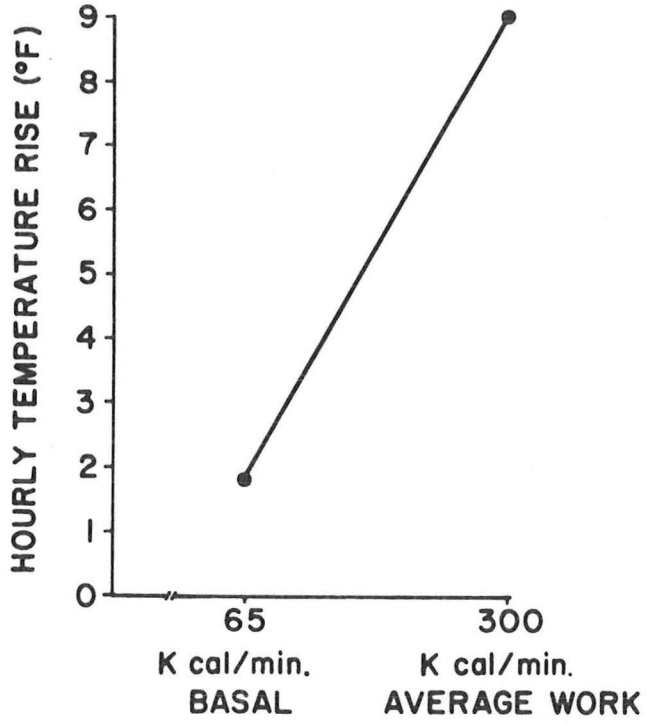
Two studies exemplify the thermal effects produced by work. Assmussen and Bøje (2) showed that during intense physical exertion, deep muscle temperature rose higher than 106° F.

Rowell and his associates (3) performed a critically important study of 11 nonheat-acclimatized, untrained young men, designed to examine hepatic-splanchnic blood flow while exercising at the highest metabolic rate they could endure for one hour in a hot atmosphere (120°F, 77°F wet bulb temperature) at work loads requiring about 50% of their maximal oxygen uptake. Effective hepatic blood flow was subnormal. Remarkably, temperature of hepatic venous blood rose as high as 107° while the simultaneous core temperature was 104°. These observations emphasize the point that metabolic oxidation in the liver as well as in skeletal muscle may occur at a rate sufficient to produce core hyperpyrexia even though this would not be indicated by measurements of rectal temperature alone. In Rowell's studies, (3) the same gradient existed between inferior caval blood and rectal temperature indicating that blood flowing from the lower extremities during exercise exceeded rectal temperature significantly. However right atrial temperature was 0.8°F less than rectal temperature.

Heat loads generated from the foregoing sources must be dissipated if thermal damage to the body is to be avoided. Similar to mechanisms of exogenous heat gain, heat dissipation also occurs by radiation and convection. However, if environmental temperature is equal to or higher than that of the body surface, heat can be lost only by vaporization of sweat. By this means, each 1.7cc of sweat vaporized will remove 1 kcal of heat. Maximum rates of vaporization are related to dryness as well as air movement. In a hot climate, the limits of the body's ability to dissipate a heat load, is therefore a function of its capacity to sweat as well as a function of the environmental capacity for vaporization of sweat. The maximum sweat rate in an untrained, unacclimatized man may attain 1.5 L/hour (4). While complete vaporization of this quantity of sweat could theoretically relieve an 882 kcal heat load (1500/1.7=882), such physical efficiency is never attained since 20% or more of sweat is lost by dripping (5) and such sweat rates cannot be sustained. In a practical sense, even under conditions favoring maximal vaporization of sweat, the upper limits of heat dissipation are approached at caloric expenditures of 650 kcal/hour. Indeed, studying heat stress in young soldiers in a dry, hot, desert climate, Adolph (6) showed that rectal temperature rose 4.5°F after running for 30 minutes at an expenditure of 680 kcal/hour.

When the environmental temperature is equal to or exceeds that of the body and the air is saturated with moisture, a progressive rise of body temperature is unavoidable. This is illustrated in Figure 1. Thus, even under basal conditions, body temperature will rise at a rate of 2°F/hour. More impressive, the rise under a moderate work load expenditure of only 300 kcal/hour will exceed 9°F/hour (7). This physical fact bears direct relationship to the clinical observation that once sweating ceases in an individual subjected to heat stress, the subsequent appearance of frank hyperpyrexia occurs with dramatic rapidity.

RELATIONSHIP OF BODY TEMPERATURE RISE
TO HEAT PRODUCTION IN A NEUTRAL ENVIORMENT



The most important defense against hyperthermia is dependent upon the cardiovascular system.

Of itself, work results in a massive shunting of blood to skeletal muscle (8). Quantitatively, muscle blood flow varies in direct proportion to the degree of work and ranges from 1 cc per 100 g muscle/minute at rest up to more than 20 times this value during intense exercise. The ideal 70 Kg man possesses 35 Kg of skeletal muscle. If he runs while carrying a heavy load so as to utilize approximately 20 Kg of his muscle, the possible shunt could be as high as 4 liters or more per minute.

The major fuel for muscular contraction during exercise is muscle glycogen. As glycogen is broken down, many smaller intermediary products are formed, all of which exert a powerful osmotic activity. Thereby, glycolysis induces movement of water from plasma in quantities averaging 10% or more of the inflowing arterial volume. (9)

As the temperature of venous blood leaving the working muscle rises, it is delivered to hypothalamic centers which immediately induce dilatation of skin vessels as well as secretion of sweat by the sweat glands. This is the so-called Benziger reflex. (10) In classical experiments, Benziger showed that perfusion of carotids with

warmed blood induced a rise of peripheral blood flow in relation to the rise of temperature and that this was followed by active sweating. As proof that sweating is not mediated by blood flow, he showed that it occurred under such conditions even if a tourniquet is placed on the arm sufficiently tight to occlude arterial flow.

As blood and body temperature rise during work with the attendant rise of blood flow to muscle and skin, profound shock would occur were it not for intense splanchnic vasoconstriction (11).

Hellon and Lind (12) showed that simple exposure to heat induced a rise of forearm (cutaneous) blood flow from 4 cc/100 ml/min at rest to 12 cc/min of forearm volume.

Nevertheless, vasoconstriction in the splanchnic bed is inadequate to compensate for the combined losses of plasma water into muscle, repartitioning of blood flow to muscle and skin, and losses of extracellular fluid volume in the form of sweat. In other words, the increased vascular capacity resulting from dilatation of vessels in skeletal muscle and skin and the loss of extracellular fluid as sweat is not sufficiently filled by splanchnic vasoconstriction. The net effect is a sharp diminution of effective arterial volume.

The central circulatory response to the fall of effective arterial volume is (a) a decrease of venous return, (b) an increase of heart rate and (c) a decrease of stroke volume. If the heart rate and venous return are adequate, (d) minute cardiac output may remain the same or rise but if sufficient hyperthermia occurs, stroke volume as well as cardiac output will fall sharply.

Gold (13) conducted an extremely hazardous study on volunteer subjects exposed in the laboratory to dry heat for either two hours at 54.5°C (130°F) and others for one hour at 71.1°C (160°F). He showed that exposure to severe heat was accompanied at first by a hyperkinetic circulation and as heat storage rose, mean venous pressure rose from 40 to nearly 200 mm. H_2O. Cardiac output was estimated in one subject. It rose from a resting value of 10.6 L/min to 16.9 L/min during heat exposure and as deterioration appeared, it fell to 6.4 L/min. Each subject was removed from the heat chamber when collapse was judged to be imminent, on the basis of abnormal sensations such as lightheadedness and a facial color change from pinkish red to almost ashen grey.

At this point many of the subjects began to cease sweating. Gold suggested that the primary event in the circulatory collapse of heat pyrexia was high output cardiac failure and the cessation of sweating results from the rising venous pressure.

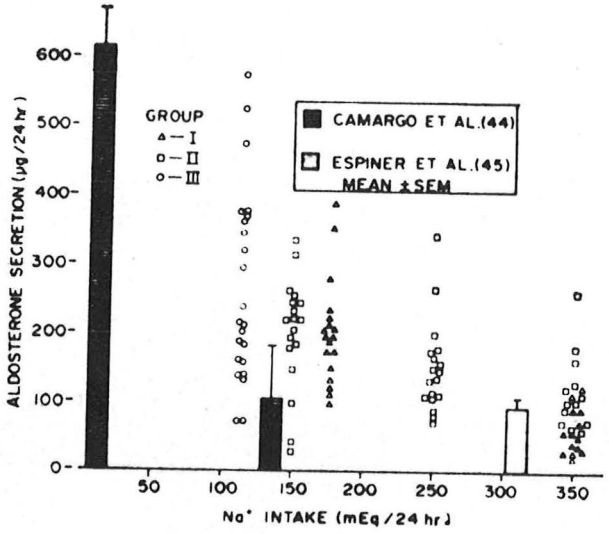
Rowell and his co-workers (14) performed another detailed study of 10 unacclimatized, untrained men comparing their hemodynamic responses to 50-80% maximal exercise in temperatures of 78°F and 110°F. Their studies showed the following results:

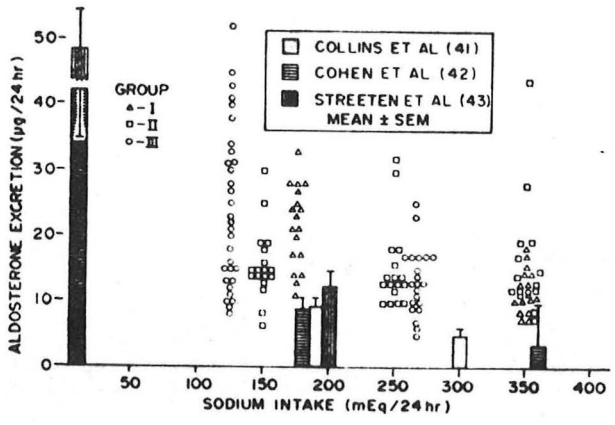
	78°F	110°F	p
O_2 Consumption (ml/kg/min)	36.4	36.0	NS
Cardiac output L/min	19.8	18.6	<0.001
Central Blood Vol L	1.34	1.21	<0.001
Heart rate beats/min	174	195	<0.001
Stroke volume ml	114	95	<0.001
Rectal temperature °F	100.8	102.9	<0.001

Williams and his associates (15) demonstrated that as an individual performs work at a level approaching his maximum oxygen utilization under conditions of high environmental temperature, requirements for augmentation of cardiac output to maintain skin and muscle blood flow are met only by additional cardio-acceleration. Under these conditions stroke volume and eventually minute cardiac output fail.

Major Endocrine Responses to Heat Stress

Although not completely evaluated, the major endocrine responses to work and/or acute heat exposure probably consist of activation of the renin-angiotensin system (16) and increased production of aldosterone (17). In my own studies conducted in young men in basic military training in hot weather (18), plasma renin activity often exceeded 2000ng/100 ml in samples collected before arising in the morning even when Na intake exceeded 300 mEq/day. Similarly, in terms of Na+ intake, both excretion as well as secretion of aldosterone were above normal. . This response per se is probably of critical importance for the process of acclimatization.





Growth hormone may also play a critical role in man's defense against effects of heat. It has been shown that both physical work as well as exposure to heat are potent stimuli for release of growth hormone (19).

It has been conclusively demonstrated that growth hormone produces a sustained retention of salt and water (20). Its action could conceivably be equally important to that of the renin-angiotensin aldosterone mechanism in acquisition of the heat acclimatized state.

Plasma cortisol concentration rises briefly during exposure to intense heat or during hard physical work (21). However, this response is not seen in the acclimatized physically trained man. In contrast to aldosterone, excretion of 17-hydroxycorticosteroids or 17-ketosteroids into the urine do not change as a consequence of acclimatization or training (17).

Renal Functional Response to Heat Stress

The renal response to hard work in the heat has been well characterized. Neither glomerular filtration rate nor renal plasma flow change upon simple exposure to moderate heat. However, even under cool environmental conditions hard physical work is regularly attended by pronounced diminution of glomerular filtration rate and renal plasma flow. These changes are markedly accentuated if work is undertaken in a hot environment and are reflected by rapid diminution of sodium and water excretion (22, 23).

PHYSIOLOGICAL FEATURES OF A HEAT ACCLIMATIZED PHYSICALLY CONDITIONED MAN

The following is a quotation from a classical description of heat acclimatization written by William Bean (24) based upon his observation of soldiers training in the California desert during World War II.

> When fit, adequately trained young men are exposed to a high temperature and high relative humidity, they are incapable of work for long periods. Compared with their performance in a temperate environment the pulse is higher, internal and skin temperatures are higher, and the blood pressure, especially in the erect position, is unstable. The face and upper part of the body are flushed, the eyes and nasal mucosa may be injected, causing lacrimation and sniffles; hands and feet exhibit edema; the rate of sweating increases considerably. There is a sense of overwhelming oppression which rapidly takes the spirit out of men. Trifling work is fatiguing and more burdensome work rapidly leads to exhaustion. A throbbing headache may develop and reach cruel intensity. Dizziness

occurs and is accentuated by the standing position. Dyspnea may be a problem. Thirst, which rapidly becomes intense if water is withheld, proves a guide to needed water replacement, since the loss is never voluntarily replaced during work. Nausea, vomiting, and loss of appetite are commonplace. Lack of coordination reduces efficiency. Eyes become glazed and stare vacantly. Apathy may be interrupted by outbursts of irritability. Judgement and morale decline. Occasionally, hysteria or hyperventilation with tetany may add their bizarre signs and symptoms. The walking man may collapse and the standing man may faint. Unwillingness to continue work and the onset of physical disability may rapidly disorganize a well-disciplined and efficient unit. Such a severe and alarming illness has commonly produced almost complete ineffectiveness.

Contrast with this picture that of the same man after four or five days of work in the heat. He now performs his work with only slightly higher pulse and temperature than in a comfortable environment. He is cheerful, alert, and vigorous. No longer does he exhibit the flushed, sometime edematous skin and engorged mucous membranes of earlier exposures. He can stand without fear of syncopy even after four hours of continuous work. Water is drunk eagerly although thirst is still not an adequate incentive for complete fluid replacement. Sweating continues at a rapid rate somewhat greater than on the first exposure. Thus, the essential gains of cardiovascular-thermal acclimatization have been made, though improvement may continue at a slow rate for days or weeks.

In Table III are shown the physiological features of a heat acclimatized and physically conditioned man.

I. CARDIOVASCULAR

- ↑ Maximal cardiac output
- ↓ Heart rate with given load
- ↑ Stroke volume

II. RECTAL TEMPERATURE

- ↓ Elevation with exercise

III. SWEAT

- ↑ Volume with given stimulus
- ↓ Na+ concentration

PHYSIOLOGIC FEATURES OF A HEAT-ACCLIMATIZED, PHYSICALLY - CONDITIONED MAN

IV. ALDOSTERONE PRODUCTION

Sustained rise

V. FLUID VOLUME CHANGES

↑ ECV
↑ PV
↑ TBW

VI. METABOLIC EFFICIENCY

↑ O_2 extraction
↓ Heat production with given load

VII. KIDNEY

↑ Glomerular filtration rate

There are three critical cardiovascular adaptations which have been shown to occur under conditions of a given unit of heat stress which permit an individual to perform work comfortably in a hot environment (25). These include 1) an increased maximal cardiac output, 2) a decrease in the peak heart rate, and 3) an increased stroke volume (14, 26). These adaptations facilitate more efficient delivery of heated blood from muscle and viscera to the body surface where it can be dissipated to the environment. A classical feature of the heat acclimatized state is a lower rectal temperature elevation with a given quantity of exercise. This results not only from the enhanced ability of the cardiovascular system to propel blood and thereby facilitate heat dissipation but also constitutes an important reflection of the increased metabolic efficiency acquired by physical training per se. Thus, it is well known that with advanced physical training, oxygen utilization for a given unit of work rises. In skeletal muscle, most oxygen utilization takes place in mitochondria. A large body of evidence has accumulated during the past few years showing that not only are mechanisms of oxygen delivery to muscle increased by training but there also occurs a marked increase in the density of mitochondria per unit muscle mass (28). Since energy production (ATP synthesis) is nearly 20 times more efficient by oxidative metabolism as opposed to anaerobic metabolism, these recent observations would explain the increased oxygen utilization with training and provide a strong chemical-structural correlation as a mechanism underlying enhanced metabolic efficiency.

Another major feature of the heat acclimatized state is a drastic alteration in the composition and volume of thermal sweat. The first recognition that sweat sodium concentration diminishes as an individual becomes acclimatized to heat is credited to

Dill and his associates (29). Their observations have been amply confirmed and the fact that sweat sodium concentration becomes lower and that the volume of sweat produced in response to a given work load rises have become physiological hallmarks of the heat acclimatized state. However, it seems to be a common experience by those performing work in a hot climate that sweat production during initial exposures to heat is much more voluminous than that occurring after acclimatization has occurred. This disparity between non-scientific impressions and physiological observations made by climatologists showing that sweat production in response to a given work unit in the heat rises as a consequence of acclimatization may have some basis in fact. Thus, nearly all physiological studies of heat acclimatization demonstrating increased sweat production during the acclimatizing process have been conducted under artificial conditions in the laboratory and usually have been no longer than two weeks duration. In this context Adam and his associates (30) studied the effects of standardized heat exposure on a large number of British troops over a period of six months. They noted that during the first two weeks the amount of sweat increased in response to given heat stress but over the following five month period there was a progressive decline of sweat output. The same conclusion has recently been cited by Dasler and his associates (31). The bulk of evidence would suggest that the diminished sweat production in response to a given work load after prolonged acclimatization to heat is probably the result of enhanced metabolic efficiency induced by training and is a reflection of a lesser quantity of endogenous heat production for the same amount of work.

A large body of evidence has accumulated over the past fifteen years showing that aldosterone excretion into the urine is higher during acclimatization to heat and indeed is probably higher in subjects living in tropical environments than in those living in temperate environments. (17)

There is also good evidence that increased production of aldosterone is essential for the acclimatization process to occur. Robinson and his co-workers (32) have shown that a large intake of sodium chloride may suppress the normal decline of sweat sodium concentration in response to heat exposure. These studies were conducted under conditions of minimal heat stress and thus probably were not applicable to natural acclimatization to heat in which intense physical work is a component. Our own studies (18) have shown that aldosterone excretion in the urine as well as aldosterone secretion remains inordinately high not only in individuals training in the heat but also under the same conditions of training during cool weather.

Impressive evidence indicates that the diminished sodium concentration of thermal sweat is due solely to the action of aldosterone. This effect has been proven experimentally by Ladell (33).

These authors have shown that under conditions of exogenous administration of desoxycorticosterone or aldosterone as well as in individuals naturally acclimatized to heat, that administration of spironolactone leads to a prompt rise of sweat sodium concentration. Sweat gland responsiveness to exogenous aldosterone is somewhat sluggish in comparison to its action on the kidney. Thus the renal response to

aldosterone occurs within a period of hours whereas the decline in sweat sodium concentration requires one or two days to appear and does not reach its full effect for a period of five or more days (34).

The volume of extracellular fluid and plasma rise sharply during acclimatization to work in the heat. The first demonstration of a relationship between climate and blood volume was provided by Barcroft and his associates (35). These individuals showed that blood volume during a voyage from England to the tropical latitudes of Peru expanded 17% as the ship traveled south. Studies confirming that such changes occur were performed by Bazett (36).

Wyndham and his associates (37) demonstrated that plasma volume, extracellular space and total body water rose in correlation with the increased cardiac output during the process of acclimatization to heat and proposed that these changes in body fluid compartments were probably a response to increased production of antidiuretic hormone and aldosterone. They noted an average plasma volume expansion of 7.4%, a 3% rise of extracellular fluid volume and a 7% increase in total body water. Alteration of body fluid compartments as a result of exposure to heat or performance of work in the heat has been carefully reviewed by Bass and Henschel (38).

In a recent study (18) a group of nine military recruits undergoing basic training in a moderately warm climate showed a mean rise of extracellular fluid volume of 9.6% as measured by radiosulfate distribution and an increase of total body water by 6.7% as measured by dilution of tritiated water.

Based upon studies extending over many years Conn (34) has made major contributions to current concepts of the physiological state of acclimatization to heat and has made an analogy of this state to that following prolonged exogenous administration of aldosterone in normal man. Thus, in an individual consuming a normal quantity of sodium chloride, administration of aldosterone or desoxycorticosterone leads to sodium retention by the kidney, a modest weight gain and decreased concentration of sodium in sweat. After several days, a new steady state is achieved during which sodium excretion reappears in the urine in accordance with intake, however maintaining body water compartments at a modestly expanded state. This so-called renal escape, i.e. reappearance of sodium excretion into the urine despite continued administration of aldosterone, does not occur in the sweat glands. Thus, unsuppressed excretion of sodium into the urine in the presence of unrelenting sodium conservation by sweat glands closely resembles characteristic findings in normal man following acclimatization to heat.

Exogenous administration of desoxycorticosterone does not induce acclimatization as determined by usual measurements in response to heat stress (39). However, a more recent study by Braun and his associates (40) showed that in terms of certain hemodynamic and thermal responses to exercise in the heat conducted on human volunteers, aldosterone did exert a favorable effect. Reasons were cited that aldosterone possesses an inotropic effect on the heart which is not possessed by DOCA.

HEAT ILLNESS

Historical Data

Wakefield and Hall reviewed the historical background of physical disease resulting from excessive environmental heat in 1929 (41). They described an incident in Peking, in July of 1743, in which 11,000 persons are said to have perished from the effects of an intense prolonged heat wave.

In 1841 on the British frigate Liverpool, while the vessel was proceeding from Muscat to Bushire, the weather gradually became warmer: double awnings were spread, the decks were kept constantly wetted and every precaution used to prevent exposure of the men. Yet in one day, from a species of coup de soleil, three lieutenants and thirty men were lost. It was stated that at one time the decks resembled a slaughter house, so numerous were the bleeding patients.[1] In 1873, Gihon described a condition known as adynamia, observed in sailors who became ill while working in ship boiler rooms and also in those subjected to sweat box punishment. The temperature in these rooms often reached 170°F. One of the earliest designations given to heat stroke was siriasis. This was based upon a biblical reference that heat stroke occurred in correlation with the appearance of the dog star, Serius, which could be seen in the twilight and followed the sun throughout the summer.

Table IV lists the currently accepted classification of heat illness (75).

Heatstroke ---------- { Following anhidrosis, febrile illness, or unqualified
Heat cramps
Heat exhaustion
1. Anhidrotic
2. Salt-deficiency (excluding heat cramps)
3. Unqualified (including water-deficiency heat exhaustion, exercise-induced heat exhaustion, and heat syncope)

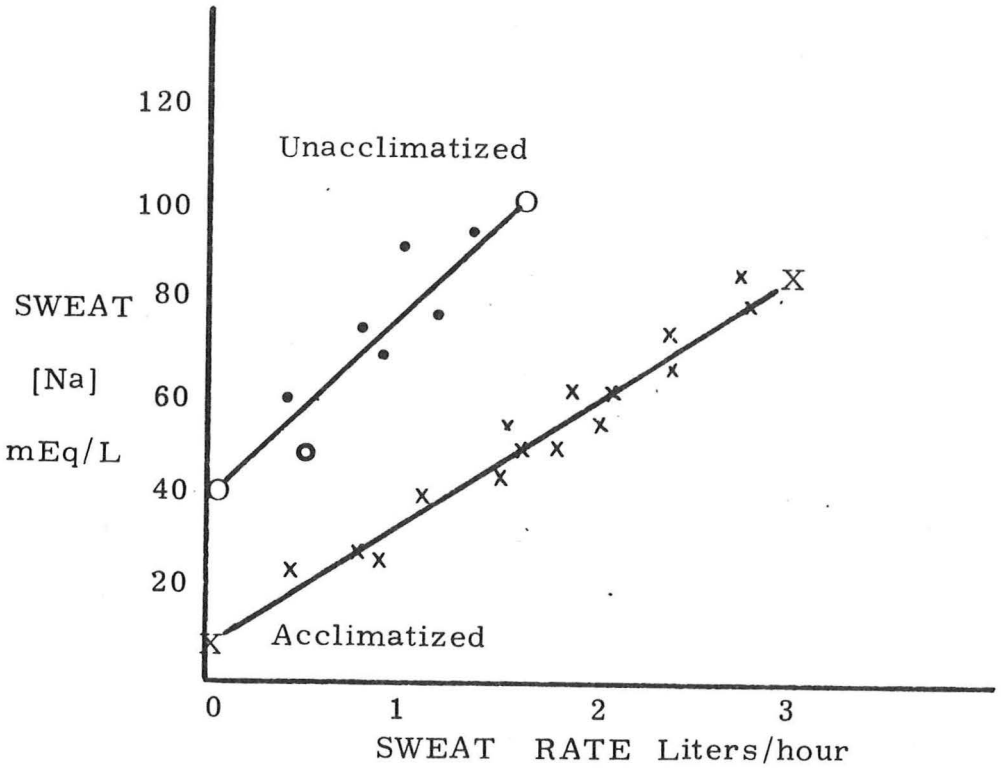
Sunburn
Prickly heat
Anhidrosis
Heat neurotic reactions (including chronic heat neurotic reaction, chronic heat fatigue, mild asthenic reaction, mild heat fatigue)
Other heat effects (including heat oedema)

[1]This apparently was either the first description of the hemorragic diathesis of heat stroke or it may have possibly represented an epidemic form of scurvy.

Three conditions are of dominant importance. They are heat cramps, heat exhaustion, and heat stroke. Since on this occasion it is intended to emphasize only the most important of the three, namely heat stroke, only a brief description will be given concerning the first two entities.

Heat Cramp

Heat cramp is an acute disorder of skeletal muscle consisting of no more than brief, intermittent, often excruciating cramps occurring in those skeletal muscles which have been used while working. They occur especially in men who are highly acclimatized to heat. Although well described by earlier observers, the classical description of this disorder was prepared by John Talbot (42). The etiology of this disorder apparently consists of an acute deficiency of sodium in the face of adequate replacement of water loss incurred by sweating. Three factors are characteristic of individuals predisposed to heat cramps. First, they are able to produce sweat in large quantities in response to hard muscular work. Second, they consume adequate amounts of water to replace the sweat losses but third, they fail to replace sodium losses. Although acclimatization is accompanied by diminished sweat sodium concentration, sodium concentration still rises sharply as the rate of sweat production rises.



However, by virtue of his ability to produce larger volumes of sweat, which is a hallmark of acclimatization to heat, such a person is endangered by the capacity to loose larger quantities of sodium than an unacclimatized person.

EFFECT OF HARD PHYSICAL WORK ON SODIUM EXCRETION IN SWEAT

	Max. Sweat Rate (L / hr)	[Na] at High Rate (mEq/L)	Max. Na Loss (mEq/hr)
UNACCLIMATIZED	1.5	100	150
ACCLIMATIZED	2.5	70	175

Within the context of the currently accepted definition of heat cramps, if any symptoms or findings co-exist other than simple muscular cramps, the disorder automatically falls into the category described as heat exhaustion.

Heat cramps tend to occur toward the end of the working day while walking home or having arrived, upon relaxing or taking a cool shower. The paroxysms of painful cramping involve muscles used in the patients occupation, tend to last no more than a few minutes and ordinarily disappear spontaneously. Rarely,heat cramps involve muscles of the anterior abdominal wall simulating an acute surgical abdomen. Although one might suspect that muscle necrosis and myoglobinuria could conceivably follow severe episodes of muscle cramps, to my knowledge this possibility has neither been examined nor reported. Similarly, the possibility that creatine phosphokinase activity or other enzymes may rise thus reflecting muscle damage in this condition has not been examined. Most individuals who sustain heat cramps soon discover that ingestion of salt is successful in their prevention. In the event of severe, repeated, unrelenting cramps, oral or intravenous salt solutions rapidly relieve all symptoms.

Heat Exhaustion

This is the most common clinical disorder associated with a high environmental temperature. While it may seem naive to state that it tends to occur during heat waves, it is to be noted that heavy sweating incident to intense muscular work even in temperate climates may lead to profound losses of body water or sodium chloride

and in turn culminate in every conceivable symptom and finding characteristic of classical heat exhaustion.

Classically, one may divide heat exhaustion into two distinct forms; viz., heat exhaustion associated with predominant dehydration and heat exhaustion associated with predominant salt depletion (7).

Heat Exhaustion Due to Predominant Water Depletion

Early studies examining the physiology of this condition were reported by Adolph (6). Any individual working in a hot environment does not spontaneously replace the volume of water lost by sweating and maintains a negative water balance which averages one or two percent of his total body weight (7). Classically, heat exhaustion due to predominant water loss occurs when the supply of water is limited or unavailable. Thus, soldiers or laborers in a hot desert climate and infants or enfeebled adults who are unable to express their desire for water, may become seriously water depleted while retaining normal stores of body sodium. As a result, hypertonic dehydration occurs. Symptoms of this disorder include intense thirst, fatigue, weakness, discomfort, anxiety, and impaired judgment. Marked central nervous system dysfunction eventually becomes prominent manifested by hyperventilation, parathesias, tetany, agitation, hysteria, muscular incoordination and in some patients, frank physcosis. Terminally, patients demonstrate dilerium, hyperthermia, and coma. It is well recognized that this form of heat exhaustion is treacherous and if unrecognized or untreated, terminates in frank heat stroke. Physical examination shows signs compatible with dehydration. Body temperature is almost invariably elevated. Under such conditions, should circulatory failure or a convulsion supervene, the rate by which body temperature rises is accelerated and frank heat stroke rapidly supervenes.

Heat Exhaustion Due to Predominant Salt Depletion

The classic clinical description of salt depletion was contributed by McCance (44, 45). Heat exhaustion due to predominant salt depletion occurs when large volumes of thermal sweat are replaced by adequate water but no salt. It differs from heat cramps in two major respects, viz., it is accompanied by systemic symptoms and tends to occur in unacclimatized persons. Significant dehydration or weight loss do not occur and as a consequence the volume of urine and sweat remains normal. In contrast to heat exhaustion due to water depletion these patients tend not to complain of intense thirst since interstitial fluid volume contracts and the intracellular space expands. Plasma volume, due to the oncotic pressure of serum proteins, tends to be better maintained than interstitial volume.

Symptoms of heat exhaustion due to salt depletion consist of profound weakness, fatigue, severe frontal headache, giddiness, anorexia, nausea, vomiting, diarrhea, and skeletal muscle cramps. As in heat cramps, painful muscular contractions tend to occur in those muscles fatigued by means of work and are apt to be precipitated by

administration of large quantities of water. Such patients appear haggard and demonstrate pallid, clammy and inelastic skin. Hypotension and tachycardia are prominent findings. In contrast to heat exhaustion due to water depletion, body temperature usually remains normal or subnormal but if dehydration supervenes as a result of vomiting, body temperature may rise. Sodium chloride deficiency in these individuals may exceed 1000 mmoles.

Treatment of heat exhaustion is fairly simple and consists of administration of either normal saline or isotonic glucose solutions in accordance with the proportion of salt or water losses. On rare occasions, hyponatremia may be of sufficient magnitude to elicit symptoms typical of water intoxication. Under such circumstances the intravenous use of hypertonic sodium chloride solutions is warranted.

Heat Stroke

Heat stroke is a catastrophic disorder characterized by hyperpyrexia, delirium, coma, and anhidrosis. Hyperpyrexia herein described refers to a rectal temperature exceeding 106°F.

Although heat stroke is the most uncommon of the three major disorders associated with heat stress, it is without question the most important since it may occur in virtual epidemic form, carries up to 80% mortality and in many of those surviving imposes severe persistent disability.

There are a number of factors which increase the risk of heat stress injury. These are enumerated on Table VI. Since the most critical determinant of man's defense against environmental heat resides in the integrity of his cardiovascular system, any cardiovascular disease under these conditions could constitute a threat to his survival. The role of the heart in the pathogenesis of heat stroke was first recognized by Adolph in 1923 (46). Burch and his associates (47, 48) have published widely on the adverse effects of environmental heat in patients with congestive heart failure. They examined the effects of high temperature (90°F) and high humidity (75%) on 23 patients in congestive failure. As might be anticipated, their failure became more overt, cardiac output failed to rise normally, some developed angina pectoris with electrocardiographic changes and some demonstrated a rise of venous pressure.

A second broad factor increasing the risk of heat stress injury is chronic disabling disease of virtually any form but especially long standing diabetes mellitus, chronic alcoholism, or malnutrition. A number of disorders associated with impairment of sweat production have been associated with a higher incidence of heat stroke. These disorders include miliaria (prickly heat), sweat gland injury or necrosis which has been reported to follow acute heat stroke (49) and barbiturate poisoning (50). The latter might explain the occasional association of heat stroke in patients intoxicated with barbiturates. Sweat gland entrapment may occur with scleroderma (51) or in patients who have survived after extensive dermal burns. Obstructive periductal lymphocytic infiltration has been described in an elderly diabetic patient with fatal

heat stroke (52). Sweat glands may be absent in patients with ectodermal dysplasia (53) and malfunction of sweat glands in patients with cystic fibrosis (54) are known to increase their susceptibility to heat stroke. Impaired sweat production occurs in patients with congestive heart failure and in those receiving certain pharmacologic agents. These include drugs used in the treatment of patients with Parkinsonism (55), atropine (56), and other anticholinergics, phenothiazines and antihistamines (57).

In otherwise healthy individuals inadequate acclimatization is always an important factor predisposing to the onset of heat stroke. Lastly, the potential importance of potassium deficiency in the pathogenesis of heat stroke has arisen (58, 59) because of the common findings of hypokalemia and other evidence suggestive of depletion of this ion in individuals who produce large volumes of sweat in response to hard work in hot climates.

Implications of Potassium Deficiency in Heat Stroke

Of 121 reported patients with acute heat stroke whose serum potassium concentration was measured at admission, a value below 3.5 mEq/L was observed in 46% (58, 61-67). Although simple exposure to heat may be accompanied by hyperventilation, respiratory alkalosis and hypokalemia (68), performance of hard physical work in the heat almost invariably is accompanied by hyperkalemia due to release of potassium from muscle (69). Severe lactic acidosis (arterial blood pH 6.9, lactate 11.2 mmoles/L) has been identified in patients with stress-induced heat stroke (70). Although acute acidosis may induce shifts of potassium from cells to plasma (71), serum potassium and blood lactate concentration have not been measured simultaneously in any patient with acute heat stroke.

During World War II, Ladell (72) observed that a number of British troops in the Libyan desert became intensely polyuric after prolonged exposure to the hot climate. In some, urine volumes exceeded 8 liters per day and did not diminish after injection of posterior pituitary extract. Some of these men developed classical heat stroke. Edholm observed daily urine volumes exceeding 10 L under similar circumstances (73). Although potassium measurements were not made in these men, vasopressin-resistant polyuria is a feature of kaliopenic nephropathy and therefore, the manifestations displayed by these men could have conceivably been the result of potassium deficiency.

Sobel and his associates (74) demonstrated vacuolar changes in renal tubular epithelium, hypokalemia and polyuria in a number of Air Force basic trainees who sustained acute heat stroke.

Several investigators have estimated potassium balance during acclimatization to heat. Bass and his co-workers (25) examined young men exposed to 12 hours each day at a temperature of 120°F, relative humidity 28%, and estimated an average daily potassium loss of 15 mEq in excess of intake. When exposed to heat, work consisted only of walking for four 30-minute periods daily.

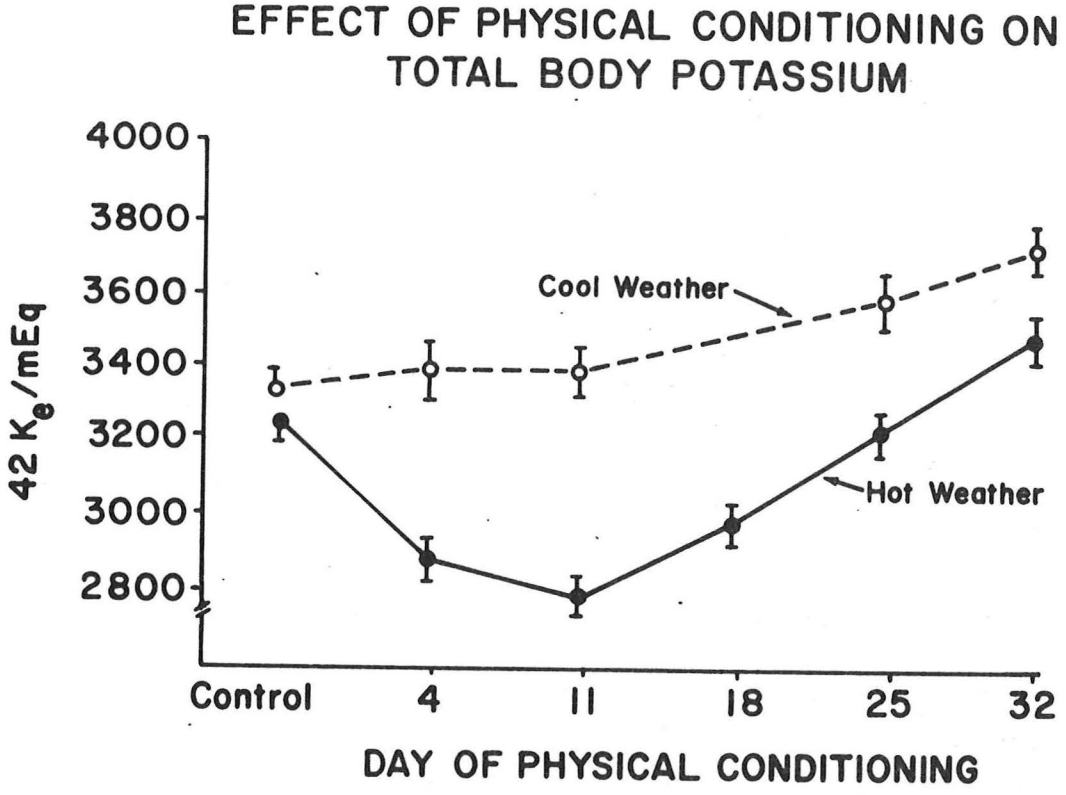
Gordon (76) exposed two volunteer subjects to 88°F, 40% relative humidity for six hours daily, five days per week for three weeks, while they ingested 25 mEq of

potassium daily. On each day of the study, the subjects vigorously exercised on a bicycle for thirty minutes alternating with 30-minute rest periods. Potassium deficiency in these two subjects was 161 and 192 mEq.

Frank hypokalemia did not occur in either of the latter studies.

The level of physical activity in the studies discussed (25, 76) did not approach that undertaken by young athletes or military recruits who are at high risk to develop heat stroke. These men have been shown to secrete up to 12 L of sweat per day and since potassium concentration in sweat may average 9 mEq/L, potassium losses in sweat exceeding 100 mEq per day could readily occur. Since dietary intake of potassium seldom exceeds 100 mEq daily, excretion of potassium in urine and feces could, consequently, generate a severe deficit in a relatively short period of time.

Accordingly, a study was designed to measure serial values for total body potassium in healthy, unacclimatized young men undergoing basic military training in the hot summer and in the cooler winter months (18). As indicated in Figure 3, those studied in the hot weather sustained a mean potassium deficit of 517 mEq by the 11th day of their training.



In comparison, those studied in cool weather showed an expected steady rise of total body potassium coincident with their increase of muscle mass. All subjects had been maintained on a constant diet containing 100 mEq of potassium throughout the periods of observation. In those who became deficient, despite large losses of potassium in sweat at the time they were deficient, potassium excretion into the urine was inappropriately high and ranged from 46 to 75 mEq per day. Simultaneously, the concentration ratio of Na/K in their sweat was very low which reflected activity of aldosterone on sweat glands. Finally, excretion and secretion of aldosterone and in many instances plasma renin activity appeared to be high with respect to sodium intake. Based upon these studies, we concluded that intense physical work in the heat stimulates higher production of aldosterone than would occur in nonexercising subjects on similar sodium intakes. Similar to the phenomenon of mineralocorticoid escape, such overproduction of aldosterone in the presence of conditions permitting excretion of sodium into the urine could facilitate continued excretion of potassium by the kidney despite serious potassium depletion. Consequently, the kidney played a role in the genesis of potassium depletion in those subjects.

Rhabdomyolysis in Heat Injury

Rhabdomyolysis occurs very commonly in young men with stress-induced heat injury. It has been observed in a number of patients with potassium deficiency of diverse causes especially when it occurs in conjunction with retention of sodium.

Potassium is a potent vasodilator and since its concentration in muscle interstitial fluid rises sharply during exercise, it is thought to play an important physiological role in exercise hyperemia (77). Using the dog, we recently examined the possibility that during exercise, 1) potassium ions might not be released from potassium-deficient muscle; 2) that muscle blood flow would not rise; and 3) that ischemic necrosis would follow. Our results confirmed these postulations and suggest that potassium deficiency might contribute to the high incidence of rhabdomyolysis observed in young men under conditions of prolonged physical exertion.

Additional studies in progress show that potassium deficient dogs demonstrate a sharp fall of cardiac output and develop acute pulmonary edema with exercise (Figure 4).

If these observations can be extrapolated to potassium-deficient men performing sustained hard work, they could explain not only the occurrence of muscle necrosis by ischemia but also suggest that potassium deficiency could impair his cardiovascular performance sufficiently to prevent adequate heat dissipation. In support of this, it has been well-demonstrated in experimental animals that potassium deficiency in conjunction with sodium loading may readily induce myocardial necrosis (85) as well as impairment of cardiac performance (86). As a consequence, potassium deficiency could conceivably be responsible for rhabdomyolysis as well as hyperpyrexia. This hypothesis is illustrated in Figure 5.

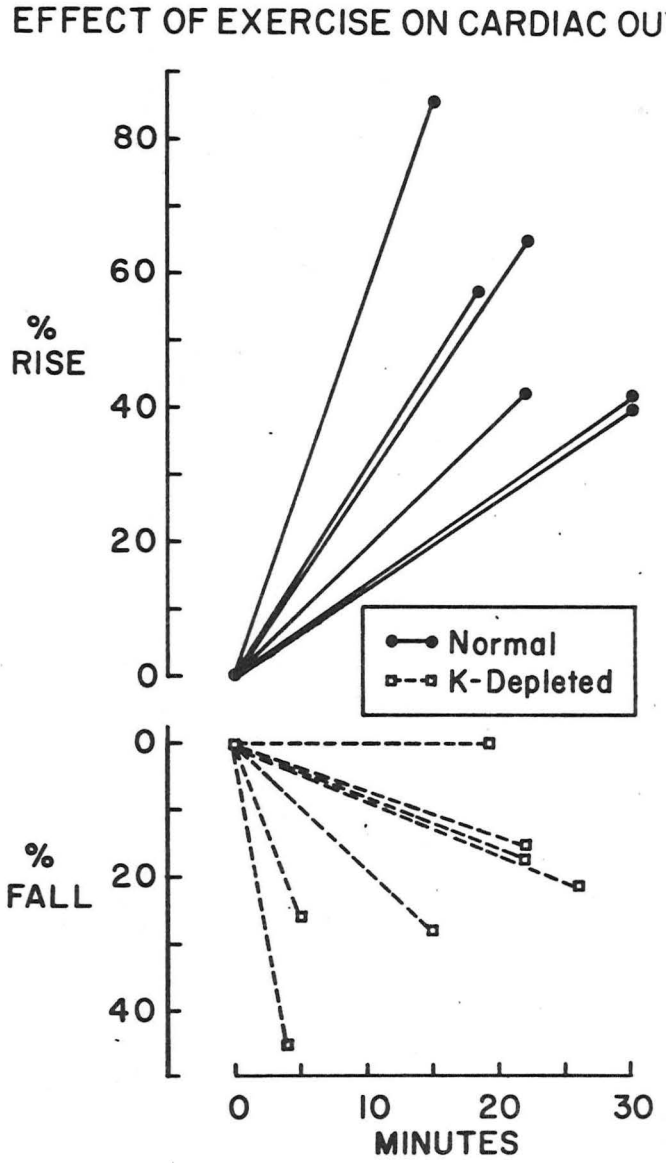


Figure 4

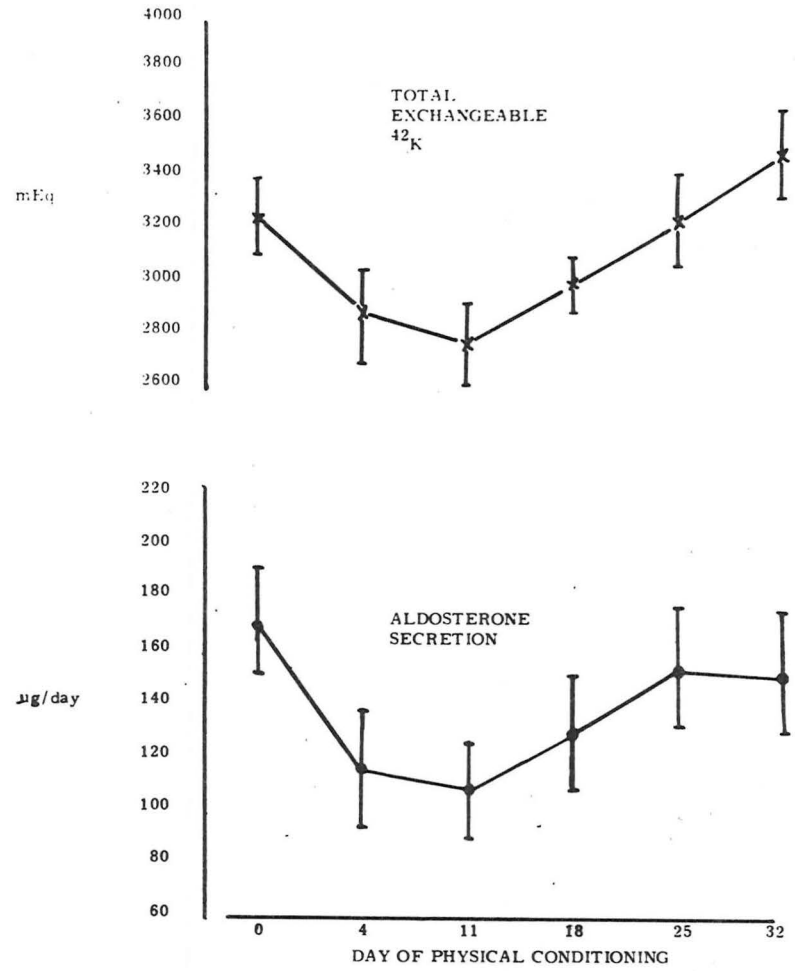


Figure 5

Clinical Spectrum of Heat Stroke

Classical Heat Stroke

Clinical descriptions of classical heat stroke are based upon observations generally made by several authors on clusters of cases occurring during heat waves. Typical of the latter were reports by Ferris and associates (65), Austin and Berry (63), and more recently by Levine (64). In the report by Ferris, et. al. (65), all cases occurred within eight consecutive days during which temperatures ranged between 102 to 106°F. Of his 44 cases only three occurred in patients under the age of 40 years. Two of those three were alcoholics and the other had an acute respiratory infection superimposed upon post-partum anemia and malnutrition. In 100 selected cases reported by Austin and Berry (63), most patients were above 60 years of age. Eighty-four per cent had cardiovascular disease and 30% had previous histories of admissions to the hospital for alcoholism.

Levine (64) reported on 25 patients with fatal hyperpyrexia whose average age was 78.4 years. 72% had arteriosclerotic heart disease and 12% had hypertension or hypertensive heart disease.

The foregoing reports are considered to be typical of circumstances preceeding that form of heat stroke observed during sustained waves of high environmental temperature. Thus after several days of temperatures often exceeding 100° or when environmental temperature is perhaps lower but accompanied by high relative humidity, that portion of the population who are aged, chronically ill or enfeebled will be at high risk. A point to be strongly emphasized in the pathogenesis of heat stroke in this group of patients concerns the character of environmental heat. Namely, not only are the temperature and humidity high but both are usually sustained throughout the day and night for several days. Thus, active perspiration is continuous but eventually fails, body temperature rises rapidly and classical heat stroke rapidly supervenes.

Prodromal symptoms in these patients may be absent, the first manifestation being sudden collapse. Other patients develop weakness, dizziness, nausea, and fainting spells for a period of two or three days before their collapse. Some patients complain of frontal headache, weakness and a feeling of excessive body heat. Muscle cramps may occur but are unusual since sodium deficiency is not characteristic. In patients who survive who are able to recall their prodromal period, about half state that sweating ceased before the onset of their collapse.

Some patients who develop this form of heat stroke have undergone a prodrome characteristic of predominant water depletion heat exhaustion. This is especially prominent in populations of nursing homes or other chronic invalid care facilities where attendant care is marginal and therefore provision of adequate water to restore extensive losses of sweat are not provided.

The classical physical findings of heat stroke, namely hyperpyrexia, coma and hot, dry skin, are based upon observations made on patients like these. Specifically, the notation in the reports of Austin and Barry (63), and Ferris and his

associates (65), that sweating was totally absent in 100% of their patients and in 84% of the patients reported by Levine (64), has established the clinical findings of hot, dry skin as a virtual pre-requisite for the diagnosis of heat stroke. Moreover, anhidrosis in such patients has led to the notion that fatigue of the sweating mechanism occupies the key position among factors thought to play a role in the pathogenesis of classical heat stroke.

Based upon clinical observations that patients with heat stroke commonly display a hot dry skin, Thaysen and Schwartz (78) and later Schwartz and Itoh (79) showed that during prolonged exposure to the heat, the rate of sweat secretion for more than 6 hours could not be sustained despite a rising body temperature. Furthermore, the sweat volume response to methacholine was markedly blunted and finally, the local response to methacholine in patients with heat stroke was only 1 to 2% of that observed in normal subjects. They concluded that their findings indicated "fatigue" of the sweat glands and suggested that this phenomenon played a role in the pathogenesis of heat stroke. This view has been challenged by Gilat and his associates (80) who noted that even when so-called sweat gland fatigue had occurred, the rate was substantially higher than values observed at rest. They argued that since the sweat rate had not fallen substantially, this so-called fatigue cannot be considered important in the pathogenesis of heat stroke. The same authors have also leveled criticism at the suggestion made by Ladell (81) that hyperthermia per se is the cause of sweat gland fatigue. Gilat and his co-workers (80) studied the change of rectal temperature in eight highly-trained, heat acclimatized Israeli soldiers during a march of 31.5 kilometers while carrying a standard load of 35 kilograms. Five of the eight had rectal temperatures ranging from 41.5 to 42.4°C. (106.7 - 108.3°F) upon completion of the march. They were allowed rest stops and water. Dehydration averaged only 0.9 L. Active sweating had persisted in all. Three were europhoric and restless. At the time of the hyperthermia all were considered to demonstrate early, albeit transient symptoms of heat stroke. Consideration of these data and their observation on 38 cases of exertion-induced heat stroke in which sweating was observed despite hyperpyrexia, indicate that sweat-gland failure is not always the critical factor in all patients with heat stroke.

Careful consideration of both views concerning the possible importance of sweat gland fatigue and its etiologic role in the pathogenesis of heat stroke leads one to conclude that under certain circumstances both authors are right since (a) sweat gland fatigue and failure must exist since many patients, especially the elderly with classical heat stroke, have dry hot skin without evidence of sweating and (b) that the subjects forming the basis of Gilat's observations where healthy young men performing virtually superhuman feats for which adequate heat dissipating means were not available. In this latter group, the total duration of physical activity required to produce hyperthermia is usually measured in minutes or hours whereas elderly patients with classical heat stroke who have anhidrosis usually have been sweating at least for a day or more and therefore are more likely to incur failure of the sweat mechanism.

Exertion-Induced Heat Stroke

Descriptions of classical heat stroke as described in invalids or in the elderly population stand in sharp contrast to observations made during and since World War II. Analysis of the literature from that point forward gives one the impression that the majority of cases occur in association with events which increase endogenous heat production and have clearly established that sweating persists in more than 50% of the total number of cases. Thus, it is clear at the present time that fatal heat stroke can occur in perfectly healthy, highly acclimatized and highly physically conditioned individuals provided their physical means to dissipate heat is prevented. This is illustrated by the following case.

Case Presentation

A 20-year-old football player was brought to the emergency room after collapsing during practice. Several hours before, he was noted to become extremely irritable and for no apparent reason, provoked arguments and made threats to several of his close friends. Thereafter, he babbled incoherently, and ran wildly about the field before collapsing. Football practice had been underway for ten days. The temperature had not been above 90°F but the peak daily humidity exceeded 50%. Physical examination showed that he was totally unresponsive with hot, flushed, and moist skin. His pupils were equal in size, widely dilated, and did not respond to light. Eye grounds were normal. Rectal temperature was greater than 108°F.: pulse rate 160 per minute, blood pressure 80/0, respirations were deep at a rate of 30/min. While on the examining table cooling was effected by placing the patient in a wake of a large fan, and by rubbing him with ice for 90 minutes until his rectal temperature reached 102°. Upon cooling, his blood pressure rose to 100/60. Thereupon, the patient became tremulous and had a series of grand mal seizures. These were followed by a rise of rectal temperature to 107°. Sweating did not appear. One hour later, he became frankly cyanotic and although only 800 cc of fluid had been administered intravenously, he showed signs compatible with frank pulmonary edema. Reinstitution of cooling measures and intermittent positive pressure respiration produced improvement.

Laboratory findings showed a white blood cell count of 18,000 with 82% polys, and a platelet count of 46,000. Serum potassium was 2.7 mEq/L and total CO_2 8.9 mmoles/L. Blood pH was 7.19 and pCO_2 28 mmHg. On the second day, the urine was scanty in volume, dark and showed a positive test for heme pigment. Serum transaminase activity was above 4,000 units. CPK was above 2,000 units.

During the following 18 hours, although the patient's temperature was kept below 102°, he did not emerge from his comatose state. Babinski reflexes and clonus were present bilaterally. Widespread petechial hemorrhages were evident. His ECG showed ST-T changes compatible with acute posterior myocardial ischemia. On the following day, 34 hours after admission, scleral icterus was observed. Total urine output since admission had been only 400 cc. Due to a rapidly rising BUN, hemodialysis was performed. Upon its completion, the patient suddenly had another convulsive seizure and expired. During the seizure, serum potassium concentration had risen

from 4.2 to 8.0 mEq/L.

This case illustrates several important points: 1) that frank heat stroke occurs in otherwise healthy young men even though sweating has not ceased; 2) in heavily-built individuals who achieve higher levels of muscular work, hyperthermia is often severe. This may be correlated with widespread hemorrhagic necrosis involving skeletal muscle, myocardium, liver, kidney and brain; 3) in severe cases, shock and acute pulmonary edema have been observed before fluid replacement and presumably indicate acute left ventricular failure. The possibility that lactic acidosis-impaired left ventricular function in this patient should be considered (82); 4) death commonly occurs as a result of acute hyperkalemia either following a convulsive seizure or as a result of extensive rhabdomyolysis; and finally 5) hypokalemia is common and in these individuals who have been sweating profusely for a week or more, probably represents serious potassium depletion.

Such cases of fulminating heat stroke classically occur among those subjected to sustained, intense physical activity in hot climates. In these patients, metabolic heat production either supersedes their capability of heat dissipation despite favorable environmental conditions or cannot be dissipated because of clothing which prevents vaporization of sweat. A good example of the latter is the football player whose leatherlined gear may cover 30% or more of his body surface and the demonstration by Mathews (83) that under such conditions, strain due to heat stress may be increased markedly.

Many such cases of effort-induced heat stroke have been observed in military recruits (58, 60, 62, 66, 74) as well as in highly trained soldiers whose requirements for performance exceed human tolerance (61, 80).

In civilian settings, besides the tendency for such cases to occur in young football players during pre-season conditioning in the late months of summer (84), severe, fulminating, exertion-induced heat stroke with rhabdomyolysis has also been noted in cases of amphetamine poisoning (84) acutely agitated psychotic patients (67) and perhaps of greatest importance, in patients experiencing alcoholic withdrawal. The following cases are further illustrative.

A 21-year-old Vietnam veteran was admitted to the Psychiatry Service on August 7, 1969, because of hyperactivity, poor judgment, insomnia, agitation, and confusion. He was treated with large doses of thorazine, cogentin, and prolixin. He remained confused and hyperactive and on the afternoon of August 13, complained of dryness of his mouth. The next morning he was hot, dry and could not be aroused. His rectal temperature exceeded 108°. His blood pressure was 60/40, pulse 140 and regular, temperature 110° by thermistor, respirations 36. The right pupil was fixed and dilated and measured 8 millimeters. The left pupil was fixed and measured 4 millimeters. He was totally unresponsive to deep pain and showed generalized flaccidity. Blood gases showed a PO_2 of 89, PCO_2 17.5, pH 7.4, and oxygen saturation 96%. Serum sodium concentration was 136, potassium 4.2, chloride 103, total CO_2 19, total

protein 7.1, albumin 4.9, calcium 6.5, total bilirubin 1.5, BUN 29, SGOT 1,120, hemoglobin 18.4 g%, platelet count 10,000. His prothrombin time was 24 seconds with a control of 13 seconds. His partial thromboplastin time was 49 with a control of 35. Fibrinogen was 287 mg %. The urine showed the presence of myoglobinuria.

The patient's temperature was lowered to 102° by rubbing with ice bags. Despite cooling his blood pressure did not respond and it was necessary to use infusions of norepinephrine, aramine, and isuprel to maintain the pressure. Heparin therapy was instituted. Repeat serum electrolyte determinations showed a sodium of 135, potassium 2.7, chloride 95, and total CO_2 14. Over the next three days the patient displayed convulsive seizures and showed evidence of progressive renal insufficiency. He expired on the third day following the onset of heat stroke.

Comments

This patient's heat stroke was considered to have resulted from physical exhaustion incident to psychotic agitation and the absence of air-conditioning superimposed on the usual hot summer weather of Dallas. His overwhelming endogenous heat load produced by continuous physical activity could not be dissipated. Finally, his ability to dissipate heat was probably impaired by the use of drugs known to impair sweating.

Case #3

This patient was a 45-year-old painter admitted in October, 1969, for treatment of a vertebral fracture sustained in a fall. He had been a known alcoholic for many years and had been treated previously for delerium tremens.

Initial physical examination showed localized tenderness over the spine and impaired motion of the lower extremitites due to pain. A slight tremor of the outstretched hands was evident. He was placed on a Foster frame. Initial laboratory data were within normal limits. During the first two hospital days, the patient displayed anorexia and vomited several times after meals. On his third hospital day he became irrational and disoriented requiring restraint and sedation. Physical examination showed a constant tremor, severe agitation, and extreme generalized sweating. He was treated with paraldehyde and chlorpromazine. Laboratory findings at this time showed a serum potassium concentration of 2.8 mEq/L, sodium 137, chloride 95, and total CO_2 32 mmoles/L. Notes by ward personnel described persistant drenching sweats. The patient was given 2 to 3 L of intravenous fluids per day. On the evening of the fourth day he passed a small quantity of benzidine positive urine which on electrophoresis indicated the presence of myoglobin. His serum was clear. Blood drawn that evening showed a serum CPK activity greater than 1,000 units and SGOT greater than 2,000 units.

On the fourth hospital day the patient had a convulsive seizure. His rectal temperature immediately thereafter was found to be 107°F. Sweating was still present. Although cooling was accomplished rapidly the patient remained unresponsive, flaccid and anuric. Extensive muscular edema appeared. He expired on the fifth hospital day.

Comments

This case illustrates again that heat stroke can occur in hospitalized patients whose disease and/or treatment impair mechanisms by which heat can be dissipated. The patient had classical delerium tremens accompanied by persistent overactivity producing an overwhelming endogenous heat load. Undoubtedly, this was complicated by dehydration due to inadequate fluid replacement, vomiting and profuse diaphoresis. Though the patient displayed no evidence or findings suggestive of alcoholic myopathy at the time of admission such a condition might have been a predisposition to acute muscular injury following prolonged agitation and convulsive seizures. Potassium deficiency might be implicated in this patient's rhabdomyolysis.

Major Pathology of Heat Stroke

A detailed description of the pathology in fatal cases of heat stroke was published by Malamud, Haymaker, and Custer (60).

Myocardial damage is common. Subendocardial hemorrhages are common and tend to occur beneath the left interventricular septum. Fragmentation and rupture of muscle fibers is also common. We have observed extensive transmural myocardial infarction in a young man with stress-induced heat stroke (58). Careful dissection of all coronary vessels at the time of autopsy disclosed no evidence of occlusion.

Evidence of kidney damage is extremely common in patients with acute heat stroke. Mild proteinuria and modest abnormalities of the urinary sediment are found in virtually 100% of these patients. However, in patients with severe hyperthermia, especially when induced by physical exertion, acute renal insufficiency occurs in approximately 25% of cases. In contrast, in patients who develop classical heat stroke as a result of simple exposure to high temperature, acute renal insufficiency occurs only in 5% of cases. In patients whose heat stroke is induced by physical effort, a large array of conditions exist which could conceivably contribute to the pathogenesis of acute renal failure. Thus, they may be partially dehydrated, excrete an acid urine, are often hyperuricemic despite excreting larger quantities of uric acid than normal into their urine (88). Uric acid nephropathy has been observed in such patients. Secondly, potassium deficiency may exist and has been regarded by certain authors as capable of depressing glomerular filtration rate and renal plasma flow as well as inducing tubular damage (89). Third, the effects of myoglobinuria in the presence of a concentrated, acid urine are well known in their capacity to induce acute tubular necrosis. Finally, the possibility of glomerular injury consequent to disseminated intravascular coagulation has been well described (90).

Although at one time acute renal failure in patients with heat stroke was considered to be irreversible, subsequent observations have proven that this is not the case. Most patients apparently sustain no more than acute tubular necrosis and with modern techniques of management apparently recover fully. A recent report by Kew and his associates (90) has described a subtle progressive impairment of renal function

in four patients who recovered from heat stroke, who on renal biopsy demonstrated interstitial nephritis. The cause of this finding was not apparent. However, consideration might be given to the possibility that these effects are the outcome of tubular or interstitial damage due to urate nephropathy.

Damage to the central nervous system in heat stroke is a universal finding in fatal cases. These findings generally consist of edema, patchy congestion and diffuse petechial hemorrhages. The hypothalamus is not ordinarily damaged. Striking changes occur in the cerebellum which shows marked deterioration of Purkinje cells. In all cases parenchymal changes of the central nervous system occur in direct relationship to the severity and duration of hyperthermia. The predominance of alterations in cerebellar structure correspond to the clinical picture of central nervous system damage in patients who survive severe heat stroke. These patients' findings resemble cerebellar attaxia with marked dysarthria and dysmetria.

Evidence of liver damage is very common (91) and jaundice occurs commonly in patients surviving more than two days. In approximately 5% of cases, jaundice may become intense. Ordinarily patients who survive show no residual damage of liver function.

Evidence of skeletal muscle damage or rhabdomyolysis, displayed by elevation of creatin-phosphokinase activity in serum and myoglobinuria, occurs in a large percentage of patients whose heat injury is induced by intensive physical exertion. Although release of myoglobin from muscle may be accompanied by extreme hyperkalemia and consequently poses an extreme hazard to life, those who survive do not show a permanent abnormality of skeletal muscle function. To my knowledge, rhabdomyolysis has only been observed in patients whose heat stroke followed physical exertion. This includes hyperpyrexia following delirium tremens or severe convulsions.

Petechial hemorrhages and ecchymoses occur commonly in the skin. Electron microscopic studies have disclosed pathological alterations of the subcellular components of sweat glands (49) which might explain the occasional observation that patients who have survived severe heat stroke display a residual impairment in their ability to sweat, and therefore demonstrate a persistent susceptibility to the effects of environmental heat.

Coagulation disorders in fatal heat stroke are common. These changes have been characteristically attributed to increased capillary permeability, impaired production of clotting factors by the liver and thrombocytopenia (92). In 1962, Shibolet (93) pointed out that hypofibrinogenemia and severe fibrinolysis occur in heat stroke. Since that time characteristic features of dissiminated intravascular coagulation have been confirmed by several authors (94). It is now well-recognized that this process occurs very commonly in severe cases of heat stroke and indeed may be responsible in large part for the widespread tissue damage observed in this condition.

Hypercalcemia and metastatic calcification in patients with heat stroke has been reported by Leonard and Nelms (95). Their patients were three marine recruits who sustained widespread muscle damage with heat stress injury. Although hypercalcemia could be the consequence of dehydration, since it has been noted by others to occur during the diuretic phase of acute renal failure, in these instances it appeared before the onset of diuresis and always seemed to be related to antecedent muscle or soft tissue injury or both. Moreover, in a case described by Leonard and Nelms (95), biochemical abnormalities suggestive of hyperparathyroidism were observed. Renal biopsy in this patient demonstrated nephrocalcimosis. Parathyroid hormone concentration was elevated.

Acid base disturbances are common features accompanying acute heat stroke. Although normal men, when exposed to a high environmental temperature characteristically hyperventilate and may, as a consequence, develop hypokalemia and hypophosphotemia as a concommitent of respiratory alcolosis, patients with acute heat stroke are generally acidotic. In virtually every incidence in which appropriate measurements have been made the acidosis has been due to accumulation of lactic acid (Ruppert, 95). Such a finding could be explained by circulatory shock with diminished perfusion of muscle as well as enhanced lactate production from skeletal muscle due to pronounced muscular activity. Finally, lactate production by the liver could also increase during severe exertion consequent to gluconeogenesis. This was observed to attain rather astronomical proportions during heat stress by Rowell and his associates (3).

Treatment of Heat Stroke

Successful management of patients with acute heat stroke depends on recognition and rapid lowering of body temperature. The classical means by which body temperature is lowered is by immersion in a tub of ice water during which time several attendants rub the patient briskly to promote diffusion of heat into the cold water. When rectal temperature falls to a level of 102^{o} the patient should be removed from the ice water otherwise his temperature may become subnormal. This treatment is much easier to recommend than accomplish. Anyone who has performed cold pressor tests is well aware of the pain eventually experienced during prolonged immersion of his hands in ice water. Such a practice rapidly becomes totally intolerable to the attendant. Moreover while the patient's temperature is falling, it is a common experience that grand mal convulsions occur which are commonly accompanied by expulsion of feces and vomiting often complicated by aspiration of gastric contents. If this should occur while a patient is being massaged in a bathtub full of ice water the entire scene deteriorates into an intolerant mess.

An equally effective and convenient method to reverse hyperpyrexia is to place the patient on a bed covered by a large rubber sheet under the margins of which have been placed rolled towels to create a shallow pool. In this position, vigorous massage with ice while the patient is in the wake of a large fan will effect cooling as rapidly as the total immersion method. A thermister probe should be inserted high in the

rectum in order to monitor core temperature. As in all such emergencies adequate airway and oxygen should be provided. Hypotension, which may occur as a result of the pronounced peripheral vasodilatation during hyperpyrexia, will often respond to cooling alone. If such a patient receives large quantities of saline or plasma expanders while hyperthermic, subsequent cooling and peripheral vasoconstriction may overload the central circulation and produce acute pulmonary edema. On the other hand, if hypotension persists after cooling, appropriate agents used in therapy of cardiogenic shock should be administered since the patient may have myocardial damage from heat injury, per se, or lactic acidosis. Due to the common occurrence of focal myocardial hemorrhages and hypokalemia, digitalis preparations should be used very cautiously if at all. In the event that shock does not respond to cooling, volume expansion may be attempted with saline or plasma volume expanders. In the latter regard, it is probably inadvisable to use dextran due to its propensity to coat platelets and induce hemorrhage. This is especially important since the majority of patients with acute heat stroke are thrombocytopenic.

If thrombocytopenia is associated with hemorrhagic manifestations or other evidence of disseminated intravascular coagulation, such as prolonged prothrombin time, prolonged partial thromboplastin time or diminution of fibrinogen concentration in plasma, anticoagulation with heparin, 1 mg/Kg every six hours, should be given strong consideration.

The utilization of vasopressor drugs may be attempted cautiously. Most authorities recommend avoidance of norepinephrine in view of the intense peripheral vasoconstriction following its use which in turn impairs heat loss and therefore may reestablish hyperthermia.

Acute renal failure should be anticipated in such patients if shock has occurred or if there is evidence of rhabdomyolysis. In this event, measures to increase urine flow such as mannitol or furosemide should be used early. If renal failure exists, extreme hyperkalemia due to widespread tissue destruction should be anticipated and accordingly regular electrocardiographic monitoring for the effects of hyperkalemia and frequent measurement of serum electrolytes are in order. It should be emphasized that patients who develop acute renal failure in the wake of heat stroke are usually extremely catabolic due to the widespread tissue necrosis and display rapidly advancing azotemia which may be sufficiently severe to preclude adequate management by peritoneal dialysis (96). Therefore, if facilities for hemodialysis are not available strong consideration should be given to transferring the patient to a hospital where such facilities are available.

The potential benefit of chlorpromazine in patients with heat stroke is unsettled. Chlorpromazine, especially in conjunction with meperidine, has been used as a "lytic cocktail" to induce hypothermia. Based upon its action to prevent shivering and possibly decrease muscle tone, oxygen utilization falls. Jesati (99) was the first to report its use as a hypothermic agent in a patient with hyperpyrexia due to acute pyelonephritis. In conjunction with application of ice bags to the body surface, his

patient's temperature fell from 107.8 to 102.6°F within two hours. Although equally rapid cooling can be effected by conventional measures, use of this method was noted to prevent shivering and convulsions during cooling which otherwise occur with great frequency. The dosage recommended was 50 mg intravenously at four to six hour intervals.

For the same reasons, Hoagland and Bishop (100) used promethazine in the same dosage followed by chlorpromazine in conjunction with tap water sponging. Their patients temperature fell from 109 to 102°F within 68 minutes. Coincidentally, diastolic pressure became obtainable and within one more hour, the patient was alert.

It would seem highly useful to use such an agent to preclude additional thermogenesis due to shivering or convulsions in a patient with heat stroke. It seems unfortunate that the potentially beneficial effects of chlorpromazine have not been examined in experimental animals. One must remember that chlorpromazine may occasionally cause convulsions.

Differential Diagnosis of Heat Stroke

Under ordinary circumstances little difficulty should be experienced in identifying a patient with classical heat stroke. One should not rely upon the presence of dry skin to confirm the diagnosis since a perspiring patient with hyperpyrexia is an equal candidate for tissue injury.

Hypothalamic damage resulting from heat stroke is uncommon. However, hyperthermia may occur in patients with hypothalamic lesions. Chesanow (.) has pointed out that "hypothalamic hyperthermia" should be suspected by 1) a uniformly high temperature without the peaks and troughs seen in sepsis; 2) anhidrosis, which may be unilateral, 3) resistance to antipyretic drugs and 4) the presence of disorders related to adjacent structures such as diabetes insipidus.

Tornblom (98) has reported several patients with idiopathic hyperthermia whose fever abated following removal of islet cell tumors.

Confusion may arise in certain cases of meningitis accompanied by an unusually high fever since on occasion patients with heat stroke demonstrate nuchal rigidity. In classical heat stroke spinal fluid may at times be blood-tinged and contain an elevated protein concentration. Pleocytosis is not a feature. Malignant hyperpyrexia is an uncommon abnormality characterized by the occurrence of extreme hyperpyrexia during or following general anesthesia (97). Susceptible individuals demonstrate persistently elevated CPK activity in serum. Since it carries a 70% mortality its prevention and/or recognition in susceptible persons is a vital importance.

Although the height of fever in acute meningococcemia, typhus, Rocky Mountain spotted fever, or falciparum malaria does not ordinarily reach levels seen in heat stroke, delirium and appearance of hemorrhagic skin manifestations certainly warrant

their consideration in the differential diagnosis. Midbrain hemorrhage may occur in certain patients with alcoholism and in some instances may be accompanied by hyperthermia. In some cases, hyperthermia would seem to be the result of the accompanying agitation and related metabolic heat production rather than a primary disturbance in thermal regulation. As evidenced by Case 3 frank heat stroke can occur as a complication of delirium tremens.

Prognosis

The physician who anticipates the occurrence of heat stroke, has a well-conceived plan for its treatment, competent help and adequate facilities will salvage the majority of such patients. Under these conditions, a successful outcome has been as high as 95%. In contrast, sporadic cases, which are often temporarily neglected and unanticipated, carry a much higher mortality. In military situations or in young football players in whom heat stroke is associated with physical exertion virtually all cases are severe, and a very high mortality rate is the rule. Illustrative of the latter statement was a report from Navy physicians charged with the responsibility of managing Marine Corps recruits who sustained acute heat stroke during basic training. Their usual mortality rate of 50% was decreased to only 30% by provision of field facilities highly equipped to effect rapid cooling.

BIBLIOGRAPHY

1. Passmore, R. and Durnin, J. V. G. A. Human energy expenditure. Physiol. Rev. 35: 801, 1955.
2. Assmussen, E. and Bøje, O. Body temperature and capacity for work. Acta Physiol. Scand. 10: 1, 1945.
3. Rowell, L. B., Brengelmann, G. L., Blackmon, J. R., Twiss, R. D., and Kusumi, F. Splanchnic blood flow and metabolism in heat-stressed man. J. Appl. Physiol. 24: 475, 1968.
4. Ladell, W. S. S. Thermal sweating. Brit. Med. Bull. 3: 175, 1945.
5. Consalazio, C. F., Johnson, R. E., and Pecora, L. J. Physiological Measurements of metabolic function in man. McGraw-Hill, Inc., New York, 1963.
6. Adolph, E. F. Physiology of man in the desert. Interscience Publishers, New York, 1947.
7. Leithead, C. S. and Lind, A. R. Heat stress and heat disorders. Davis, Phil., 1964, p. 34.
8. Haddy, F. J. and Scott, J. B. Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol. Rev. 48: 688, 1968.
9. Schlein, E. M., Jensen, D., and Knochel, J. P. The effect of plasma water loss on assessment of muscle metabolism during exercise. Submitted to J. Appl. Physiol.
10. Benziger, T. H. On physical heat regulation and the sense of temperature in man. Proc. Nat. Acad. Sci. 45: 645, 1959.
11. Rowell, L. B., Blackman, J. R., Martin, R. N., Mazzarella, J. A., and Bruce, R. A. Hepatic clearance of indocyanine green in man under thermal and exercise stress. J. Appl. Physiol. 20: 384, 1965.
12. Hellon, R. F. and Lind, A. R. The influence of age on peripheral vasodilatation in a hot environment. J. Physiol. (Lond.) 141: 262, 1958.
13. Gold, J. Development of heat pyrexia. JAMA 173: 1175, 1960.
14. Rowell, L. B., Marx, H. J., Bruce, R. A., Conn, R. D., and Kusumi, F. Reductions in cardiac output, central blood volume and stroke volume with thermal stress in normal men during exercise. J. Clin. Invest. 45: 1801, 1966.
15. Williams, C. G., Bredell, G. A. G., Wyndham, C. H., Strydom, N. B., Morrison, J. F., Peter, J., Fleming, P. W., and Ward, J. S. Circulatory and metabolic reactions to work in the heat. J. Appl. Physiol. 17: 625, 1962.
16. Bozovic, L., Castenfors, J., and Piscator, M. Effect of prolonged, heavy exercise on urinary protein excretion and plasma renin activity. Acta Physiol. Scand. 70: 143, 1967.
17. Collins, K. J., and Weiner, J. S. Endocrinologic aspects of exposure to high environmental temperatures. Physiol. Rev. 48: 785, 1968.
18. Knochel, J. P., Dotin, L. N., and Hamburger, R. J. Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. J. C. I. 51: 242, 1972.
19. Schalch, D. S. The influence of physical stress and exercise on growth hormone and insulin secretion in man. J. Lab. Clin. Med. 69: 256, 1967.

20. Biglieri, E. G., Wathington, C. D., and Forsham, P. H. Sodium retention with HGH and its subfractions. J. Clin. Endocrinol. & Metab. 21: 361, 1961.
21. Collins, K. J., Few, J. D., Forward, T., and Giec, L. The plasma glucocorticoid response to environmental heat stress. J. Physiol. (Lond.) 194: 33-34P, 1968.
22. Radigan, L. R. and Robinson, S. Effects of environmental heat stress and exercise on renal blood flow and filtration rate. J. Appl. Physiol. 2: 185, 1949.
23. Castenfors, J. Renal function during exercise. Acta Physiol. Scand. 70: Suppl. 293, 1, 1967.
24. Bean, W. B. in Pathologic Physiology, W. A. Sodeman, ed., W. B. Saunders, Philadelphia, 1956, p. 234.
25. Bass, D. E., Kleeman, C. R., Quinn, M., Henschel, A., and Hegnauer, A. Mechanisms of acclimatization to heat in man. Medicine 34: 323, 1955.
26. Wyndham, C. H., Benade, A. J. A., Williams, C. G., Strydom, N. B., Goldin, A., and Heyns, A. J. A. Changes in central circulation and body fluid spaces during acclimatization to heat. J. Appl. Physiol. 25: 586, 1968.
27. Pattengale, P. K. Augmentation of skeletal muscle myoglobin by a program of treadmill running. Am. J. Physiol. 213: 783, 1967.
28. Gollnick, P. D. and King, D. W. Effect of exercise and training on mitochondria of rat skeletal muscle. Am. J. Physiol. 216: 1502, 1969.
29. Dill, D. B., Hall, F. G., and Edwards, H. T. Changes in composition of sweat during acclimatization to heat. Am. J. Physiol. 123: 412, 1938.
30. Adam, J. M., Collins, J. A. G., Ellis, F. B., Irwin, J. O., Jack, J. W., John, R. T., Jones, R. N., MacPherson, R. K., and Weiner, J. S. Physiological responses to hot environments of young European men in the tropics. II & III. Further Studies on the effects of exposure to varying levels of environmental stress. Med. Res. Coun. (London), RNP. REP. 55: 831, 1955.
31. Dosler, A. R. and Hardenbergh, E. Decreased sweat rate in heat acclimatization. Fed. Proc. (abstr.) 30: 209, 1971.
32. Robinson, S., Kincaid, R. K., and Rhamy, R. K. Effect of salt deficiency on the salt concentration in sweat. J. Appl. Physiol. 3: 55, 1950.
33. Ladell, W. S. S. and Shepard, R. J. Aldosterone inhibition and acclimatization to heat. J. Physiol. 160: 19, 1962.
34. Conn, J. W. Aldosteronism in man. Some climatological aspects. JAMA 183: 775-781, 871-878, 1963.
35. Barcroft, J. C., Binger, A., Bock, A. B., Doggert, J. H., Forpes, H. S., Harrop, G., Meakins, J. C., and Redfield, A. C. Philosophical Trans. Roy. Soc. 211: B, 351, 1922.
36. Bazett, H. C. The effect of heat on the blood volume and circulation. JAMA 111: 1841, 1938.
37. Wyndham, C. H., Denade, A. J. A., Williams, C. G., Strydom, N. B., Goldin, A., and Heynes, A. J. A. Changes in central circulation and body fluid spaces during acclimatization to heat. J. Appl. Physiol. 25: 586, 1968.
38. Bass, D. E. and Henschel, A. Responses of body fluid compartments to heat and cold. Physiol. Rev. 36: 128, 1956.

39. Robinson, S., Kincaid, R.K., and Rhamy, R.K. Effects of desoxycorticosterone acetate on acclimatization of men to heat. J. Appl. Physiol. 2: 399, 1950.
40. Braun, W.E., Maher, J.T., and Byrom, R.F. Effect of exogenous d-aldosterone on heat acclimatization in man. J. Appl. Physiol. 23: 341, 1967.
41. Wakefield, E.G. and Hall, W.W. Heat Injuries. A preparatory study for experimental heat stroke. JAMA 89: 92, 1929.
42. Talbott, J.H. Heat Cramps. Medicine 14: 323, 1935.
43. Adolph, E.F. and Dill, D.B. Observations on water metabolism in the desert. Am. J. Physiol. 123: 369, 1938.
44. McCance, R.A. Experimental sodium chloride deficiency in man. Proc. Roy. Soc. London, S. B., 119: 245, 1936.
45. McCance, R.A. Medical problems in mineral metabolism. III. Experimental human salt deficiency. Lancet 1: 823, 1936.
46. Adolph, E.S., Fulton, W.B. The effects of exposure to high temperatures upon the circulation in man. Am. J. Physiol. 67: 573, 1923.
47. Burch, G.E. and Hyman, A. Influence of a hot and humid environment upon cardiac output and work in normal man and in patients with chronic congestive heart failure at rest. Am. Heart J. 53: 665, 1956.
48. Ansari, A. and Burch, G.E. Influence of hot environments on the cardiovascular system. Arch. Int. Med. 123:371, 1969.
49. Baba, N. and Ruppert, R.D. Alteration of Eccrine sweat gland in fatal heart stroke. Arch. Path. 85: 669, 1968.
50. Leavell, U.W. Sweat gland neurosis in barbituate poisoning. Arch. Derm. 100: 218, 1969.
51. Buchwald, I. and Davis, P.J. Scleroderma with fatal heat stroke. JAMA 201: 270, 1967.
52. Bleisch, V. Clinicopathologic conference. A sixty-five year old woman with heat stroke. Am. J. Med. 43: 113, 1967.
53. MacQuaide, D.H.G. Congenital absence of sweat glands. Lancet 2: 531, 1944.
54. Di Sant 'Agnese, P.A., Darling, R.C., Perera, G.A., and Shea, E. Sweat electrolyte disturbances associated with childhood pancreatic disease. Am. J. Med. 15:777, 1953.
55. Litman, R.E. Heat stroke in Parkinsonism. Arch. Int. Med. 89: 562, 1952.
56. Chapman, J. and Bean, W.B. Iatrogenic heat stroke. JAMA 161: 1375, 1956.
57. Gottschalk, P.G. and Thomas, J.E. Heat stroke. Mayo Clin. Proc. 41: 470, 1966.
58. Knochel, J.P., Beisel, W.R., Herndon, JR., E.G., Gerard, E.S., and Barry, K.G. The renal, cardiovascular, hematologic and serum electrolyte abnormalities of heat stroke. Am. J. Med. 30:299, 1961.
59. Knochel, J.P. and Vertel, R.M. Salt loading as a possible factor in the production of potassium depletion, rhabdomyolysis and heat injury. Lancet 1:659, 1967.
60. Malamud, N., Haymaker, W., and Custer, R.P. Heat Stroke: A clinicopathologic study of 125 fatal cases. Milit. Surg. 99: 397, 1946.

61. Shibolet, S., Coll, R., Gilat, T., and Sohar, E. Heat Stroke: Its clinical picture and mechanism in 36 cases. Quart. J. Med. 36: 525, 1967.
62. Vertel, R. M. and Knochel, J. P. Acute renal failure due to heat injury. An analysis of ten cases associated with a high incidence of myoglobinuria. Am. J. Med. 43: 435, 1967.
63. Austin, M. G. and Berry, J. W. Observations on 100 cases of heat stroke. JAMA 161: 1525, 1956.
64. Levine, J. A. Heat stroke in the aged. Am. J. Med. 47: 251, 1969.
65. Ferris, E. B. Jr., Blankenhorn, M. A., Robinson, H. W. and Cullen, G. E. Heat stroke: Clinical and chemical observations on 44 cases. J. C. I. 17: 249, 1938.
66. Baxter, C. R. and Teschan, P. E. Atypical heat stroke, with hypernatremia, acute renal failure, and fulminating potassium intoxication. Arch. Int. Med. 101: 1040, 1958.
67. Bale, P. M., Calvert, A. F., and Hirst, E. Skeletal muscle necrosis in heat stroke. Am. J. Clin. Path. 50: 440, 1968.
68. Iampietro, P. F. Heat-induced tetany. Fed. Proc. 22: 884, 1963.
69. Kilburn, K. H. Muscular origin of elevated plasma potassium during muscular exercise. J. Appl. Physiol. 21: 675, 1966.
70. Ruppert, R. D., Newman, A., Scarpelli, D. G., and Weissler, A. M. The mechanism of metabolic acidosis in heat stroke. Clin. Res. 12:356, 1964.
71. Burnell, J. M., Villamil, M. F., Uyena, B. T. and Scribner, B. H. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and extracellular potassium. J. C. I. 35: 935, 1956.
72. Ladell, W. S. S., Waterlow, J. C. and Hudson, M. F. Desert Climate. Physiological and clinical observations. Lancet 2:491, 527, 1944.
73. Edholm, O. G. Comments on symposium on heat acclimatization. Fed. Proc., 23: 907, 1963.
74. Sobel, S., Johnson, W. C., McPhaul, J., McIntosh, D. A., Miller, Jr., W. E., and Rhoades, E. R. Renal mechanisms in heat stroke. Clin. Res. 11: 252, 1963.
75. Weiner, J. S. and Horne, G. O. A classification of heat illness. Brit. Med. J. 1: 1533, 1958.
76. Gordon, R. S. and Andrews, H. L. Potassium depletion under heat stress. Fed. Proc. 25: 1372, 1966.
77. Kjellmer, I. Potassium ion as a vasodilator during muscular exercise. Acta Physiol. Scand. 63: 460, 1965.
78. Thaysen, J. H. and Schwartz, I. L. Fatigue of sweat glands. J. C. I. 34: 1719, 1955.
79. Schwartz, I. L. and Itoh, S. Fatigue of the sweat glands in heat stroke. J. C. I. 35: 733, 1956 (abstr.).
80. Gilat, T., Shibolet, S., and Sohar, E. Mechanism of heat stroke. J. Trop. Med. Hyg. 66: 204, 1963.
81. Ladell, W. S. S. Disorders due to heat. Trans. Roy. Soc. Trop. Med. & Hyg. 51: 189, 1957.
82. Wildenthal, K., Mierzwiak, D. S., Myers, R. W., and Mitchell, J. H. Effects of lactic acidosis on left ventricular performance. Am. J. Physiol. 214: 1352, 1968.

83. Mathews, D. K., Fox, E. L., and Tanzi, D. Physiological responses during exercise and recovery in a football uniform. J. Appl. Physiol. 26: 611, 1969.
84. Fox, E. L., Mathews, D. K., Kaufman, W. S., andBowers, R. W. Effects of football equipment on thermal balance and energy cost during exercise. Res. Quart. 37: 332, 1966.
85. Ginsberg, M. D., Hertzman, M., Schmidt-Nowara, W. W. Amphetamine intoxication with coagulopathy, hyperthermia and reversible renal failure. Ann. Int. Med. 73: 81, 1970.
86. Darrow, D. C. and Miller, H. C. Production of cardiac lesions by repeated injections of desoxycorticosterone acetate. J. Clin. Invest. 21: 601, 1942.
87. Gale, H. H. Contractile mechanics of papillary muscles from rats with experimentally induced cardiac necrosis. Physiologist 14: 145, 1971.
88. Knochel, J. P., Dotin, L. N., Hamburger, R. J., and Mason, Jr., A. D. Exercise-induced hyperuricemia. Clin. Res. 17: 52, 1969.
89. Schwartz, W. B. and Relman, A. S. Effects of electrolyte disorders on renal function. N. Eng. J. Med. 276: 383, 1967.
90. Kew, M. C., Abrahams, C., and Seftel, H. C. Chronic interstitial nephritis as a consequence of heat stroke. Quart. J. Med. 39: 189, 1969.
91. Herman, R. H. and Sullivan, Jr., B. H. Heat stroke and jaundice. Am. J. Med. 27:154, 1959.
92. Wright, D. O. and Cuttino, J. T. Purpuric manifestations of heat stroke. Studies of prothrombin and platelets in 12 cases. Arch. Int. Med. 77: 27, 1946.
93. Shibolet, S., Fisher, S., Gilat, T., Bank, H., and Heller, H. Fibrinolysis and hemorrhages in fatal heat stroke. New Eng. J. Med. 266:169, 1962.
94. Weber, M. B. and Blakely, J. A. The hemorrhagic diathesis of heat stroke. Lancet 1: 1190, 1969.
95. Daily, W. M. and Harrison, T. R. A study of the mechanism and treatment of experimental heat pyrexia. Am. J. Med. Sci. 215: 42, 1948.
96. Nolph, K. D., Whitcomb, M. E., and Schrier, R. W. Mechanisms for inefficient peritoneal dialysis in acute renal failure associated with heat stress and exercise. Ann. Int. Med. 71: 317, 1969.
97. Kalow, W., Britt, B. A., Terreau, M. E., and Haist, C. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet 2: 895, 1970.
98. Törnblom, N. Hyperinsulinism with fatal postoperative hyperthermia. Acta Med. Scand. 170: 757, 1961.
99. Jesati, R. M. Management of severe hyperthermia with chlorpromazine and refrigeration. N. Eng. J. Med. 254: 426, 1956.
100. Hoagland, R. J. and Bishop, R. H. A physiologic treatment of heat stroke. Am. J. Med. Sci. 241: 415, 1961.