THE HYPERVENTILATION SYNDROME

by

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PREFACE

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INTRODUCTION

Advancements in the field of psychosomatic medicine have been accompanied by vigorous inquiry into the physiologic dynamics by which stress, tension, and anxiety result in symptoms, signs, and organic changes in the individual. Within this field, the hyperventilation syndrome has been found to occur so frequently, and to have such manifold effects, that a clear cut understanding of its dynamics is of vital significance.

In addition to discussing the causes of hyperventilation and its diagnostic features, the main purpose of this thesis is to discuss the pathophysiology of hyperventilation and on the basis of it, attempt to explain the origin of its clinical manifestations.

Though this thesis is mainly a review of the literature, the author has attempted to correlate diverse findings into a unified explanation. Because there has been little investigation into many aspects of this syndrome several of the conclusions reached are tentative and theoretical. The author has cited certain avenues worthy of further investigation and a few of his own preliminary studies are presented in the Appendix.

CAUSES OF HYPERVENTILATION

The most common form of hyperventilation, and the one with which we are primarily concerned, is that due to emotional factors. It occurs in the normal response to stress or tension and, along with such things as the release of adrenalin, hyperglycemia, tachycardia, and mydriasis, it represents in a primitive sense the organisms preparation for fight or flight. By washing out carbon dioxide and causing alkalosis it prepares the body for buffering the acid wastes of increased metabolism. In emotional disorders in which chronic stress and anxiety are present, hyperventilation may occur so frequently and so profoundly that its resultant effects become a prominent part of the disorder. In some patients it may appear as an isolated hysterical symptom unaccompanied by the other signs usually associated with stress.

There are other less common causes of hyperventilation. These include painful stimuli, fever, various encephalopathies, salicylate toxicity, anoxia (such as that which occurs at high altitude), an increased CO_2 level of the blood, and heart disease (1). In the treatment of the patient with hyperventilation it is therefore necessary to first rule out any possible organic cause before it is attributed to an emotional problem.

THE CLINICAL PICTURE

A. Major Signs and Symptoms

Signs and symptoms of the hyperventilation syndrome are usually rather easily recognized. The major ones may be conveniently divided into two groups:

1) A reduction in consciousness.

2) Increased neuromuscular irritability.

Under the first heading are included such things as dizziness, light headedness, giddiness, faintness, feelings of unreality, blurring of vision and rarely actual syncope. Objectively, these correlate with a decreased performance on tests involving memory, concentration, and calculation.

Those related to neuromuscular irritability include numbness and tingling - characteristically of the finger tips and perioral regions, although it may be generalized, signs of latent tetany including Chvostek and Trousseau, rarely frank tetany with muscle twitching and carpopedal spasm, and perhaps tinnitus. Spasm of specific muscles may give rise to pain in a localized area; frequently the diaphragm or intercostal muscles (1)(6).

B. Minor Signs and Symptoms

In addition to the major ones, there are numerous minor signs and symptoms.

Hyperpnea in itself is manifested in various ways. Subjective-

ly patients frequently complain of shortness of breath or a tightness across their chest and objectively they may display sighing respiration and excessive yawning, all of which contribute to their increased ventilation (6).

There are many signs and symptoms which are associated with but are not specifically a part of the syndrome. These include palpitation, "skipped beats", dryness of the mouth, dysphagia, abdominal bloating, belching, and flatulence. Patients may have generalized symptoms of easy fatigue, weakness, insomnia, and chronic exhaustion. As part of the psychic components, anxiety, tension, and apprehension are usually seen except in hysterical patients who appear quite calm (6).

C. Differential Diagnosis

In addition to individual signs and symptoms, there are other criteria which aid in the correct diagnosis of hyperventilation secondary to a functional disorder. It goes without saying that in terms of the patients present psychic dynamics and past developmental history there must be positive evidence of a functional disorder. Then too, causes of hyperventilation, other than functional, must be ruled out. As an aid to differential diagnosis, Lewis notes that organic hyperventilation syndromes, rather than following the chronic flucuating course typical of functional hyperventilation, feature more circumscribed and acute episodes often terminating in frank tetany (6).

It must also be realized that tetany, the most dramatic sign, actually is rarely present (1,6). Lewis states that peripheral paresthesia is the most consistent symptom and disordered breathing is the most common sign. One should immediately suspect that a patient is a hyperventilator if he has these two things (6). The physician must also be aware of the fact that frequently one is confronted with an atypical picture in which the respiratory component is masked by prominent symptoms referable to other systems. (6).

PATHOPHYSIOLOGY

Because hyperventilation brings about profound changes in blood chemistry which may be reflected in every region of the body bathed by the vascular system, and because it may originate as part of an anxiety state and therefore be associated with numerous responses of the voluntary and autonomic nervous systems, the entire internal environment is altered and changes are seen in almost every organ system of the body. An appreciation of these changes is requisite to an understanding of the signs and symptoms.

A. Respiratory

The initial and most significant change occurs in the respiratory system and involves a fall in arterial blood CO_2 tension. Normally, arterial blood CO_2 tension equals the alveolar air CO_2 tension (3). The normal value for alveolar air CO_2 tension is 40 mm of Hg and the CO_2 tension of expired air is 20 mm of Hg. These values are constant at basal conditions for both sexes and all ages (4). Abnormal changes are due to two variables:

1) The rate of alveolar ventilation.

2) The metabolic rate.

Each of these cause changes in the value of alveolar air and arterial blood CO_2, either directly or indirectly. Therefore, hyperventilation alone will cause a fall in the alveolar CO_2 tension

merely by its "washing out" effect, and a secondary fall in arterial blood CO_2.

The magnitude of these changes is illustrated by the fact that a single deep respiration will decrease the arterial CO_2 concentration by 5 to 7 volumes per cent and the CO_2 tension by 7 to 16 mm. of Hg. Most of the CO_2 reduction in sustained hyperventilation is accomplished during the first thirty to sixty seconds (6). It will be shown in the section on fluid and electrolytes how a reduction in CO_2 can result in alkalosis.

It is interesting to point out that hyperventilation in the presence of advanced pulmonary disease may, however, cause a rise in arterial CO_2 tension. This is explained by the fact that with advanced disease alveolar ventilation can be little improved by hyperventilation and is more than offset by the increased production of CO_2 resulting from the increased metabolism of the effort.

In the hyperventilation syndrome one sees a distortion in the normal mechanism of respiratory control. It is a well known fact that the respiratory center is driven by the level of CO_2 and not of O_2 (5). Therefore, hyperventilation with its loss of CO_2 is normally followed by a period of apnea until CO_2 again builds up to a sufficient level. Clinically, however, patients are seen who display prolonged periods of hyperventilation without apnea. It has also been shown experimentally that when hyperventilation is continued over several hours to days and the stimulus is removed, continued hyperpnea rather than apnea occurs (3). As yet, the mechanism of

this abnormality remains obscure but one may postulate several explanations.

1) Since cerebral vasoconstriction occurs with hyperventilati on (see discussion below), perhaps a decreased circulation through the respiratory center causes the intracellular gas tensions in the center to remain above normal (3).

2) Perhaps during long periods of hyperventilation the chemosensitive cells of the respiratory center develop an increasing sensitivity to small amounts of CO_2 (3).

3) Perhaps brain tissue has a decreased buffering capacity for CO_2 followi ng prolonged hyperventilation, so that a decrease in ventilation with a slight increase in CO_2 could effect a relatively high increase in pH of the respiratory center and thereby stimulate respiration more easily. The decreased buffering capacity might be explained on the basis of loss of base reserve due to a shift toward compensated respiratory alkalosis. It is of interest to point out that petit mal patients, who are known to be more sensitive to the effects of hyperventilation, have been shown to have a decreased buffering capacity of their brain tissue to CO_2 (3).

4) Continued hyperventilation without apnea may also be explained by assuming that impulses from higher centers continue to drive respiration despite the inhibitory effect of decreased CO_2. It is known for example, that lesions of the basal ganglia in a postencephalitic syndrome may cause chronic hyperventilation with persistent low CO_2 tension (7). One might assume that in an emotional disorder impulses feeding down from higher brain centers have a

similar affect.

Hyperventilation, therefore, involves a derangement in the normal mechanism of respiratory control, but the exact mechanism is not yet known.

It also appears as though the actual mechanics of breathing are impaired in these patients. They tend to demonstrate a peculiar heaving type of respiration involving mainly the upper part of the thorax and calling into play the respiratory accessory muscles. This may persist during apparently quiet breathing and flouroscopic studies have revealed the presence of a depressed relatively immobile diaphragm (6,8). It will be pointed out later how this in itself is capable of producing symptoms.

B. Cerebral

It is a well recognized fact that hyperventilation is associated with changes in the electroencephalogram consisting of an increased number of slow (low frequency) high voltage waves (1,3,9). Experiments have shown that EEG slowing correlates well with a reduction in consciousness, the latter being most marked when the frequency was reduced to below 5 cycles/sec. The affect of hyperventilation on the EEG is influenced by mumerous factors. It is more marked in children than adults, with a very rapid reduction in the CO_2 content of arterial blood, a low blood sugar, a low O_2 tension of inspired air, an erect posture, or in the presence of amyl nitrate or nitroglycerine (1). The EEG changes have no correlation with the occurence of tetany and are not significantly affected by the

injection of $CaCl_2$ (1). They therefore appear to be unrelated to tetany but are definitely related to those symptoms grouped under the heading of reduction in consciousness.

The work of Gibbs and others has shown that there is an interrelation between decreased arterial CO_2 tension, cerebral vasoconstriction, and slowing of the EEG pattern. Hypoxia and hypoglycemia probably play no role in the EEG changes seen in the hyperventilation syndrome (9).

Their studies in which cerebral O_2 arterio-venous difference was measured under various blood CO_2 tensions indicate that a decrease in arterial CO_2 tension causes constriction of the cerebral arterioles, whereas an increase in arterial CO_2 tension causes a dilatation of these arterioles (9,11). These changes appear to be specific for the brain since CO_2 changes have the opposite effect on arterioles in the extremities. Similar effects were noted by Wolff et al when the diameters of pial vessels of the cat brain were measured by direct observation. They also noted that the influence of CO_2 level on cerebral arteriole diameter almost completely obscured that of the O_2 level (10). Cerebral arteriole constriction, therefore, appears to be under the direct control of CO_2 tension. Gibbs believes that this is a homeostatic mechanism by which a constant intracerebral CO_2 tension is assured despite changes in the CO_2 tension of blood. Thus, when the arteriole CO_2 tension falls, cerebral arteriole constriction occurs thereby preventing escape of CO_2 from brain tissue. Since there is a simul-

taneous arteriole dilatation in the extremities which tends to wash out CO_2 from these areas, there is further assurance of maintaining CO_2 level in the brain in the face of an overall hypocapnea. The opposite changes occur with increased CO_2 and have the same homeostatic effect on brain tissue (9).

The magnitude of these changes is brought out in a study by Kety and Schmidt in which five normal young adult males hyperventilated for 20 - 30 minutes. Following this the group showed a mean reduction in cerebral blood flow of 35% of the mean control value. It is pertinent to the subject of this thesis that along with this, all five showed impaired cerebral function. An additional finding in this study was the fact that cerebral O_2 consumption increased 15% in subjects who actively hyperventilated but showed no change in those who were passively hyperventilated. This is attributed to the increased cerebral metabolic activity associated with active hyperventilation.

It appears as though a defect in the above mentioned homeostatic mechanism may play a role in certain clinical conditions. Gibbs has found that in patients with petit mal epilepsy, and in normals who on hyperventilating have a low threshold for EEG slowing, this mechanism is impaired; that is, there is a relative incompetence of the cerebral vasoconstrictor response to low arterial CO_2 tension and abnormal slowing of the EEG occurs during hyperventilation (9).

C. Cardiovascular

In an extensive review of the literature E.B.Brown, Jr. concludes that hyperventilation has no consistent affect on cardiac output (3).

Hyperventilation has contrasting vasomotor effects in each of the peripheral vascular beds. As mentionad before, cerebral arterioles undergo vasoconstriction (9). It would appear from studies on skin resistance, and direct observation of vessel caliber, that skin vessels also constrict during hyperventilation (9). On the other hand, major arterioles of the arms and legs, and possibly those in the splanchnic bed undergo dilatation (3)(6). Decreased CO_2 tension has an inhibitory affect on the vasomotor center which is reinforced reflexly through aortic and carotid sinus chemoreceptors. This explains the probable occurence of splanchnic vasodilatation. Constrictor responses in other vascular beds are due to the direct peripheral affect of decreased CO_2 (6).

Hyperventilation has no significant affect on Blood Pressure. This has been brought out in numerous studies in which voluntary hyperventilation was carried out for from 10 to 40 minutes (3)(11). It is interesting that the study by Kety and Schmidt showed that passive hyperventilation in anesthetized dogs and man did lower blood pressure even though voluntary hyperventilation in the unanesthetized subject did not (11). Since cardiac output does not change, blood pressure would be dependent upon the magnitude of the contrasting

vasomotor effects in the various peripheral beds. Apparently with voluntary hyperventilation the summation of these changes is such that total peripheral resistance is unchanged and therefore blood pressure remains at a constant level.

Venous return is also an important factor in considering changes in the cardiovascular system. Various studies corroborate the fact that venous return is seriously retarded by acapnia (3)(4). It has been related to a loss of muscle tonus and is referred to as "Henderson's thesis". J.J. Short has demonstrated this in several ways (4). Following three minutes of hyperventilation, the internal muscle pressure as measured by a needle placed in the relaxed biceps muscle fell from a normal of 110 mm. of H_2O to 70 mm. of H_2O, electromyography studies showed a decrease in muscle tonus, and venous pressure fell 20%. It was also found that following prolonged hyperventilation the cellular fluid of muscle increases in volume (4). This decreased venous return in the face of unchanged cardiac output may explain the tachycardia attending hyperventilation (6).

Hyperventilation causes characteristic changes in the electrocardiogram. In 1943 Thompson noted that patients with this syndrome frequently showed in their ECG an inversion of the T wave, or a depression of the S-T segment with marked lowering of the T wave, in any or all leads. He pointed out that these changes along with the precordial pain, so commonly a part of this syndrome, may lead to a mistaken diagnosis of myocardial infarction (12).

An, as yet unpublished study by Wasserburger and Lorenz describes a similar so-called "juvenile pattern". Out of 862 routine admission ECG's done on tuberculous patients entering the Veteran's Administration Hospital at Madison, Wisconsin, they found 30 patients who showed persistent RST and T wave changes and an additional 17 in whom these changes appeared after 10 - 20 seconds of hyperventilation but reverted to normal with rest. All of these patients were normotensive and had a normal cardiovascular silhouette on x-ray. The ECG changes were mainly in leads V_1 - V_4. RST segments showed coving with either elevation or depression of the proximal segment, T waves were inverted, and U waves were common in the precordial leads; but the ECG was otherwise normal. In almost all of these patients the RST and T wave alterations were exaggerated by hyperventilation. It is of particular significance that subsequent clinical evaluation and psychiatric testing revealed that 28 of these patients were suffering from major psychiatric disorders and exhibited characteristic signs of vasomotor instability, anxiety and hypochondriasis. It was found that Banthine or Pro-banthine brought about a reversal of the abnormal ECG changes and that during the period of their administration hyperventilation had no affect on the ECG. This suggests that vagal impulses are in some way related to the ECG changes seen in hyperventilation but the true mechanism is as yet obscure (13).

It is of interest that in hypopotassemia one notes ECG changes

very similar to those of hyperventilation (17). We also know that in alkalosis in general and in alkalosis of hyperventilation there is a migration of potassium out of the cells (see section on electrolytes). In Wasserburger's studies, the administration of potassium tended to prevent the ECG changes of hyperventilation. All of this suggests that the changes noted in the ECG during hyperventilation may only reflect a relative cellular potassium deficit in the heart. On the other hand, it is known that potassium potentiates the effect of acetylcholine upon the autonomic ganglion cells (5). It may be that through this potentiation potassium mediates certain changes in autonomic stimulation to the heart which in turn are reflected in the ECG. This would also explain why Banthine and Pro-banthine, being anticholinergic, reverse these changes.

Not only does hyperventilation influence circulatory dynamics, but it also influences the O_2 transport mechanism of the blood. In body tissues the dissociation of HbO_2 with the release of O_2 to the tissues is favored by an increased CO_2 tension. Conversely, a decreased tension of CO_2 causes Hb to cling to O_2 more tenaciously and can result in relative tissue hypoxia. The latter change does occur with hyperventilation. Actually, it has been shown that it is not the CO_2 concentration per se which affects the HbO_2 dissociation curve, but it is instead the pH change, since other acids will bring about the same result as when CO_2 is increased. Thus, respiratory alkalosis contributes to tissue hypoxia. This hypoxic affect is augmented in

those areas where decreased CO_2 causes vasoconstriction.

That such tissue hypoxia actually does occur has been demonstrated by Stormont and Seevers (16). They found by direct measurement that O_2 tension of the skin dropped on the average from 36 mm. of Hg to 12 mm. of Hg in dogs who were hyperventilated for 4 - 15 hours. Similar changes were noted in the O_2 tension in the peritoneal cavity. Along with these changes there was a decrease in the CO_2 tension in skin and peritoneal cavity, also determined by direct measurement. They postulated that the decreased O_2 tension was due to vasoconstriction but perhaps it is also related to the decreased HbO_2 dissociation.

Experimentally, severe and prolonged respiratory alkalosis in the dog has been found to be associated with hemoglobinemia and this has been proven to be related to the increase in blood pH (15). There is, however, no evidence that the hyperventilation seen clinically is ever severe enough to cause actual hemoglobinemia.

D. Blood Chemistry

The most complex and perhaps least well understood changes are those in blood chemistry. These are of profound significance because they may alter chemical equilibria throughout the body.

As previously noted in the section on respiration, hyperventilation causes a fall in arterial blood CO_2 tension. One experiment found it depressed from an initial value of 36.4 mm. of mercury to 16.8 after three minutes of hyperventilation, 15.0 after six minutes

of hyperventilation and partial recovery to 26.4 three minutes after hyperventilation was terminated (19). Other reports agree with these figures (3).

The profound fall in arterial blood CO_2 tension is the direct cause of a rise in blood pH. This is best understood by a consideration of the Henderson - Hasselbalch equation. The equation describes blood pH in terms of the ratio of base bicarbonate ($BHCO_3$, mainly sodium bicarbonate) to carbonic acid (H_2CO_3) in the blood. It states that blood pH = 6.1 + log ($BHCO_3$/ H_2CO_3), where 6.1 is the negative logarithm of the dissociation constant for carbonic acid in plasma when buffered by base bicarbonate and determined experimentally. In normal plasma H_2CO_3 equals 1.33 mEq./ liter and $BHCO_3$ equals 27 mEq./ liter. Therefore pH = 6.1 + log (27 / 1.33), or 7.4. It is evident that the latter ratio of 20:1, rather than the absolute values of $BHCO_3$ and H_2CO_3, is what determines blood pH. Carbonic acid content of arterial blood is determined by its carbon dioxide tension which in turn is equal to the carbon dioxide tension of alveolar air. Expressed more exactly, $H_2CO_3 = 0.0301pCO_2$, where 0.0301 equals the solubility of CO_2 in plasma expressed as millimoles / liter/ millimeter mercury of CO_2 tension and pCO_2 equals the CO_2 tension of arterial blood (or the CO_2 tension of alveolar air since the two are equal). Substituting this equation for H_2CO_3 into the Henderson-Hasselbalch equation, blood pH = 6.1 + log($BHCO_3$/$0.0301pCO_2$) Thus hyperventilation, by lowering arterial CO_2 tension (pCO_2) reduces

the denominator of the above equation and results in a rise in blood pH. This change is termed "uncompensated respiratory alkalosis" (17,3).

Numerous experiments verify the increase in blood pH (3,19,33). The details and results of an experiment on blood pH by this writer will be found in the Appendix. The following findings in an experiment by Rapoport are typical; these are mean figures on seven subjects (19).

	Arterial serum pH
Control period	7.47
After 2-3 minutes of Hyperventilation	7.68
After 5-6 minutes of Hyperventilation	7.73
6 minutes after end of Hyperventilation	7.59

The rate of change in arterial blood pH during hyperpnea is summarized by Brown. There is a rapid rise within 5 to 20 seconds and continuing during the first 2 to 3 minutes. Thereafter it increases more slowly with a maximum reached in 10 to 15 minutes. The pH returns to normal in approximately 5 minutes after hyperpnea is ended (3).

Magnitude of changes in pH depends on the blood sample taken. The change is greatest for arterial blood, intermediate for capillary blood, and least for venous blood (19). This is readily understandable because arterial blood is in direct equilibrium with alveolar air and the thick walled vessels in which it travels prevent much exchange with the body tissues. Two cases presented by Sattler et al. demonstrate the smaller magnitude of change in venous blood pH. In

one case the initial venous pH was 7.37 and rose to 7.49 after 5 minutes of hyperventilation. In another case it rose from an initial value of 7.35 to 7.55 after 12 minutes of hyperventilation (24). By comparison, these changes are less than those in arterial pH, when the duration of hyperventilation is approximately equal. Because of these differences one must be cautious not to assume that profound changes in arterial blood pH necessarily indicate actual changes in the pH of tissues. Little data is available on changes in the pH of intracellular fluid though Rapoport reports an increase in the pH of red blood cells from 7.17 to 7.34 after 6 minutes of hyperpnea (19).

As a consequence of the above rise in pH various compensatory mechanisms may come into play tending to restore blood pH to normal. Since it is the ratio of $BHCO_3$ / H_2CO_3 which must be adjusted if pH is to return to normal, a fall in H_2CO_3 can be compensated for by a proportionate decrease in plasma bicarbonate level (3,17). The level of plasma bicarbonate can be decreased in two ways. One of these is by decreasing the total plasma cation or "fixed base" though excretion and the other is by increasing the concentration of anions of acids stronger than carbonic acid ("fixed acids") An example of the latter mechanism is the effect of an increased concentration of the "fixed acid" hydrochloric acid, and is illustrated by the equation, $HCl + NaHCO_3 = NaCl + H_2CO_3$. An increased concentration of HCl would shift the equation to the right and bring about a

decreased concentration of bicarbonate (18). The kidney may aid in the compensation of respiratory alkalosis by decreasing its formation and excretion of NH_4, increasing its excretion of $NaHCO_3$, and decreasing its excretion of fixed acids. Presumably shifts between the extracellular compartment and the intracellular may also play a compensatory role (3,7,17).

Thus a decrease in plasma bicarbonate, reflected clinically by a decrease in the "CO_2 combining power", may accompany hyperventilation and this has been reported in numerous studies in which the period of hyperventilation varied from three minutes to twenty-four hours (2,3,19,20). Brown, however, believes that renal compensation for respiratory alkalosis with a decrease in plasma bicarbonate does not occur during short periods of hyperventilation. He believes that the reported fall in CO_2 combining power with short periods of overbreathing noted in the early literature is a laboratory error due to the use of separated plasma rather than whole blood for its determination (3). This is substantiated by an experiment done by Brown and others in which eight men were hyperventilated in a body respirator for from eight to twenty-four hours. They found that the CO_2 combining capacity actually <u>increased</u> during the first hour and the compensatory decrease in HCO_3 did not occur until some time after one hour of hyperventilation. It is therefore apparent that HCO_3 decreases with prolonged hyperventilation, though there is disagreement as to whether or not it does during short periods.

In contrast to the fall in plasma bicarbonate, there is a reciprocal rise in plasma chloride. In a study by Rapoport et al. arterial plasma chloride rose from a control value of 106.3 mEq./ liter to 109.2 mEq./ liter following three to six minutes of voluntary hyperventilation in normal men (19). Similar results were obtained in a study by Kerr (2). Brown, however, found no consistent change in chloride (20). In his study, Rapoport found that with the increase in plasma chloride there was an almost equal decrease of chloride in the red blood cells and therefore concludes that with hyperventilation there is a shift of chloride from the cells to the plasma. This would coincide with Kerr's observation that during hyperventilation he could obtain no free gastric hydrochloric acid (2).

One of the most striking and least explicable changes is the fall in serum inorganic phosphorous (3,19,20,33). In Rapoport's study he found that it fell from 2.4 mg./100 cc. to 1.8 mg./100cc. (19). Changes of an even greater magnitude were found by Brown when patients were hyperventilated for several hours (20), and Brown has cited similar results by several other investigators (3). An explanation for this change is not yet clear. In vitro studies on blood have shown that inorganic phosphorous (phosphate) changes in the same direction as does the hydrogen ion concentration. Perhaps phosphate shifts into the cells under the influence of an increased pH (20). Rapoport questions whether or not the phosphate change is related to altered carbohydrate metabo-

lism in response to adrenalin (19). Despite the fall in level of serum phosphate the urine shows a decreased excretion of phosphate by the kidney (3,20) so that the serum change can not be due to renal excretion and most likely involves a shift between fluid compartments.

Along with the above cited anionic changes hyperventilation brings about certain cationic changes. Various studies concur on the fact that serum sodium is decreased (19,20). This is illustrated by Rapoport's study in which serum sodium fell from a control value of 137.5 mEq. / liter to 134.2 mEq./ liter after six minutes of hyperventilation. The fact that urine shows an increased concentration of sodium with hyperventilation is evidence of the fact that the serum change is due to increased renal excretion and perhaps represents part of the above mentioned compensatory mechanisms (3,20,21).

Serum potassium on the other hand, is increased, according to Rapoport's study. He noted a change from 4.3 mEq. / liter to 4.8 mEq./ liter after six minutes of hyperventilation (19). Since urinary excretion of potassium also increased (20) there probably occurs a release of potassium from the intracellular compartment to the extracellular and subsequent excretion. This may be due to the associated release of adrenalin which in itself is known to cause a transient increase in arterial plasma potassium concentration, though alkalosis in itself is known to cause a loss of intracellular potassium.

The question of changes in blood calcium levels is a complex and not entirely answered one and will be discussed in greater detail

in the section on tetany. Suffice it to say now, that there does not appear to be any significant change in the level of total blood calcium.

Very little is known about changes in the level of blood magnesium. In one study by Kerr no consistent change was found during hyperventilation (2). Certainly this aspect requires further investigation and may yet prove to be significant in explaining changes in neuromuscular irritability.

Hyperventilation may affect various non-electrolyte constituents of the blood. Its affect on blood glucose level is debatable. Brown sites two references in the German literature and an experiment by György in which hypoglycemia was reported to have accompanied hyperventilation (3). There are reports that hyperventilation may decrease and even reverse the hyperglycemic effect of adrenalin (22). After fourteen subjects who had symptoms suggestive of anxiety or hyperventilation were hyperventilated for thirty minutes or until they had tetany, Kerr found blood sugar to be near the lower limits of normal. In the same study he found serum proteins were also at the lower limits of normal. He attributes these minor changes to the accompanying hydremia (2). According to Rapoport, blood sugar does not change in a uniform way during hyperventilation (19). In one study, lactic acid is reported to be increased during hyperventilation (23).

In terms of water balance, various experiments substantiate the fact that there is a shift of water out of the cell, into the

plasma, and eventually an increased excretion by the kidney of body water. Cellular dehydration is evidenced in Rapoport's previously mentioned study. He found that the hemoglobin concentration per red cell was increased following six minutes of hyperventilation and that the total electrolyte concentration of serum decreased by about 1.7% (19). These he believes are evidence of a shift of water into the plasma. Further substantiation is afforded by the previously mentioned finding that serum proteins are at the lower limits of normal during hyperventilation (2). Along with the relative hemodilution, several experiments show an increase in urinary volume (3,20) which would go along with the increased excretion of body water.

Changes seen in the urine include an increase in ph by as much as two or three units, an increased excretion of sodium, potassium, and bicarbonate, a decreased excretion of inorganic phosphorous and ammonia, little change in excretion of chloride, and an increase in the total urinary volume (2,3,20,21).

SUMMARY OF FLUID AND ELECTROLYTE CHANGES WITH HYPERVENTILATION

This chart is tentative and is based on experimentally verified facts as well as postulated ones.

	BLOOD		URINE
	Plasma	Cells	
pH	Increase	Increase	Increase
H_2CO_3	Decrease	Decrease	---
HCO_3^-	Decrease	Decrease	Increase
Cl	Increase	Decrease	---
PO_4	Decrease	Increase (?)	Decrease
Na	Decrease	(?)	Increase
K	Increase	Decrease	Increase
Ca(total)	same	---	---
Mg	same (?)	(?)	---
NH_4	---	---	Decrease
Glucose	Same or Decreased	---	---
Serum Proteins	Relative Decrease	---	---
Lactic Acid	Increase	---	---
H_2O	Increase	Decrease	Increase

E. Endocrine

There is reason to believe that various hormonal factors may play a role in hyperventilation. As yet there is no direct evidence of this and they may be implicated only by inference.

Since hyperventilation is seen as one of the components of stress and tension it is reasonable to assume that it is associated with a release into the circulation of increased amounts of adrenalin. Short suggests that adrenalin may actually stimulate hyperpnea through one of two mechanisms,

1) Merely by increasing the production of carbon dioxide due to its metabolic stimulation

2) By increasing the sensitivity of the respiratory center to small amounts of carbon dioxide (4).

Experimental evidence on this point is,as yet, lacking. Perhaps many of the clinical manifestations of hyperventilation are actually due to adrenalin alone or adrenalin in combination with hyperventilation.

Adrenalin may well play a role in the increased neuromuscular irritability of the hyperventilation syndrome. In itself, adrenalin is said to increase the summation of nerve impulses, have a stimulatory affect on the cerebral cortex, and act as a respiratory and cardiac accelerator (2). There are also reports in the literature that adrenalin potentiates the tetanic effect of hyperventilation (25); these will be more fully discussed under the subject of tetany. The increase in serum potassium may be caused by adrenalin, which is

known to be capable of releasing cellular potassium (19). It is also possible that hyperventilation antagonizes some of the actions of adrenalin. In experiments on pulmonary ventilation in "spinal cats" both hypo and hyperventilation caused a smaller rise in blood pressure induced by adrenalin than when ventilation was normal (22). It has also been shown that the hyperglycemic effect of adrenalin may be decreased or reversed by hyperventilation (22). The latter may explain the inconsistencies noted in studies on blood glucose during hyperventilation.

Because of distortions in the blood electrolyte pattern seen during hyperventilation one wonders whether or not the adrenal cortex might play a role in this syndrome. A discussion of this and the possible influence of aldosterone will be found further on in this paper.

F. Neuromuscular

We shall consider here only the peripheral neuromuscular changes since the cerebral ones have already been discussed. In general, hyperventilation causes an increase in neuromuscular irritability. A decreased nerve threshold and an increase in chronaxie have been demonstrated and there is augmentation of the patellar reflex (3). Muscle itself is said to undergo a loss in tonicity as evidenced by the previously cited reduction in internal muscle pressure (4). The manifestations of tetany have been

mentioned before and a discussion of its exact mechanism is reserved for a separate section. In all of these changes it is quite difficult to separate those entirely due to central and those entirely due to peripheral influences.

G. Gastrointestinal

The absence of free hydrochloric acid in gastric secretion has been found to occur with hyperpnea (2). The sympathetic stimulation occuring with hyperventilation would cause a contraction of the bowel sphincters and dilatation of the stomach (2). Aerophagia is also a common accompaniment of hyperpnea (6).

H. Urinary

Actual changes in urinary volume and make-up have already been discussed in the section on fluids and electrolytes. Kerr cites the fact that there is frequent distention of the urinary bladder and attributes this to sympathetic stimulation of the sphincters (2). There are few studies on the specific effects of hyperventilation in the gastrointestinal or urinary systems.

CORRELATION BETWEEN CLINICAL PICTURE AND PATHOPHYSIOLOGY

Having discussed the altered physiology noted in various organ systems as a result of hyperventilation, we shall now attempt to use this material as a basis for explaining the clinical manifestations of this syndrome.

A. Reduced Consciousness

We can logically group the symptoms of dizziness, giddiness, light headedness, faintness, impaired concentration and memory, feelings of unreality, blurred vision, and syncope under the general heading of "a decreased level of consciousness". These symptoms no doubt, have their origin at the cerebral level and may be considered as subjective manifestations of impaired or "depressed" cerebral activity. They correlate with the objective finding of a decreased performance on psychomotor tests, a lengthened latent period of negative after images, a reduction in hearing acuity, and a shift away from the usualness in word association (3). Further evidence that they are due to abnormal cerebral activity is the fact that they are attended by a "slowing" of the EEG tracing. The direct cause of impaired cerebral activity is most likely a decreased carbon dioxide tension in cerebral tissue which alters normal cerebral metabolic activity. Cerebral hypoxia may be an additional etiologic factor since cerebral vasoconstriction, a decrease in cerebral blood flow, and an inhibition of oxyhemoglobin dissociation are known to attend hyperventilation. It is also quite possible that the electro-

lyte changes we have mentioned, in addition to altering peripheral neuromuscular irritability, also have a direct influence on cerebral activity.

B. Paresthesias

The physiologic basis for the symptoms of numbness and tingling is most likely found in the vasoconstriction of skin blood vessels, augmented perhaps by an inhibition of oxyhemoglobin dissociation. These are symptoms common to numerous diseases in which vascular insufficiency predominates.

It is quite unlikely that they are central in origin since they do not correlate with EEG changes (6). In calcium deficiency one sees numbness and tingling of the nose, ears, circumoral region and tips of fingers and toes (17); symptoms which are very much like those seen with hyperventilation. On the basis of this, one would be very apt to attribute the paresthesias of hyperventilation to a calcium deficiency were it not for the fact that changes in blood calcium during hyperventilation have not been demonstrated. Thus in the absence of any demonstrable relation between electrolyte or EEG changes and paresthesias of hyperventilation, peripheral vascular insufficiency appears to be the most likely cause.

C. Tetany - A detailed discussion of the general subject

Tetany, when it occurs, is one of the most striking manifestations of hyperventilation. Though numerous theories have been

proposed to explain its underlying mechanism none of these are entirely adequate and fail to find complete verification in experimental studies. In order to gain further insight into this problem, it is of value to review in a general way the entire subject of tetany.

1. The tetanic state

Though the diseases in which tetany occurs are numerous, they all result in a characteristic clinical picture; one which we shall now describe. In "manifest tetany", one sees carpo-pedal spasm. This results in the so-called "accoucheur's hand", in which the hands are flexed at the wrists, fingers are flexed at the meta-carpo-phalangeal but extended at the interphalangeal joints, and thumbs are adducted into the palm. The feet are extended at the ankles and toes are plantar flexed. In addition, there may be spasm of the eye muscles and in children one may see jerking movements, generalized convulsions and laryngeal spasm. In "latent tetany", Chvostek 's sign, a twitching or spasm of the facial muscles elicited by tapping over the facial nerve in front of the ear, and Trousseau's sign, carpal spasm brought on by occluding the circulation to the extremity, are present. Increased excitability of muscles to galvanic current stimulation, Erb's sign, and Von Bonsdorff's phenomenon are also present. The latter refers to a facilitation of muscle spasm caused by hyperventilation while the circulation to an extremity is occluded. All of these changes are seen in the condition tetany, and hyperventilation is only one of its numerous causes (2,25).

2. Causes of tetany

We will now consider some of the common causes of tetany. These may be classified according to etiology and the following is an outline of these:

1. Tetany associated with a decrease in total serum calcium. (2,17,26,27,28).

   a. Hypoparathyroidism - Decreased serum calcium and increased serum phosphorous.

   b. Tetany of the newborn - Actually a form of "a" with similar serum findings.

   c. Healing stage of rickets - Decreased serum calcium.

   d. Osteomalacia - Calcium reduced and phosphorous normal or reduced

   e. Celiac Rickets and Non Tropical Sprue - Defective absorption of fat, vitamin D, and calcium.

   f. Dietary deficiency Calcium - With Vitamin D deficiency seen in cows after calving.

   g. Fixation of Calcium in tissues and exudates - Serum Calcium decreased.

      1. Acute Pancreatitis
      2. Generalized peritonitis
      3. Massive subcutaneous infection
      4. Burns during the sloughing and granulation stage.

2. Tetany associated with alkalosis (2,26). Total serum calcium is normal.

   a. Gastric tetany - Persistent vomiting, as in pyloric obstruction, causing a loss of chloride and alkalosis.

   b. Bicarbonate tetany - Caused by the ingestion of large amounts of sodium bicarbonate.

   c. Hyperventilation tetany

3. Tetany associated with binding of serum calcium.(2,26)

   a. This may be due to excessive amounts of ions capable of combining with calcium to form insoluble salts; i.e. carbonate, phosphate, oxalate, fluoride, citrate.

      (Phosphate tetany - due to injection of Na_2HPO_4 may be due either to the resultant alkalosis or to the binding of calcium by the phospate)

4. Magnesium Deficiency Tetany - It has been produced in rats, dogs, and young cattle and causes a tetany indistinquishable from calcium deficiency tetany. It has never been identified in humans.

In review, tetany can apparently be caused by a decrease in the value of total serum calcium, increased binding of serum calcium by certain anions, magnesium deficiency, or alkalosis. The mechanism of the latter is not yet clear and it possibly operates by effecting a change in the aforementioned factors. This will be discussed more thoroughly as we turn now to a more detailed consideration of hyperventilation tetany and its possible mechanism.

3. Hyperventilation tetany

In evaluating the subject of hyperventilation tetany, it is important to point out that though it is probably the best known manifestation of hyperventilation, it is actually the least common one, being a late and relatively rare symptom. (1,4). Brown et al. found that it took a profound degree of hyperventilation to produce tetany in normal subjects. They demonstrated the following relationship: minute respiratory volume necessary to cause tetany / normal minute volume = 3 (20). Nevertheless, it behooves us to explain this rare, yet striking manifestation.

Central or Peripheral in Origin

A basic question to be answered is whether hyperventilation tetany is central or peripheral in its origin.

Engel et al. found no relationship between the phenomena of a reduction in consciousness with slowing of the EEG and tetany. On the contrary, they found that tetany occurs only with longer periods of hyperpnea and that when there is marked loss of consciousness and EEG slowing, an involuntary cessation of breathing results and tetany is unlikely to occur (1). Rapoport points out that the EEG changes begin at once and progress to a maximum within 1.5 - 2.5 minutes, whereas tetany usually appears later (19). They therefore believe that it is peripheral in origin. This would be substantiated by the observation that tetany does not occur in the hand to which circulation has been occluded prior to hyperventilation (25). The latter indicating that circulatory factors can prevent tetany even though the nerve supply is intact. The Trousseau sign in itself would tend to rule out tetany as being central in origin since it would be difficult to conceive of occlusion of blood supply to an extremity as being capable of eliciting a tetanic stimulus which would start in the central nervous system and go out to that extremity.

On the other hand, there is evidence which would support the idea that tetany is central in origin. In the Swiss literature there is a study in which total conduction anesthesia of the nerves of the hand in normal subjects was obtained by local injection

of 2% procaine hydrochloride. Hyperventilation tetany was then induced but it was found that the anesthetized and motor paralyzed muscles of the palm remained flaccid. Formication, however, was experienced in the injected hand and was attributed to projection from brain centers to the periphery. The author concludes that hyperventilation tetany is mediated by the brain. He attributes it to a decreased level of ionized calcium acting centrally and points out that certain noxious agents, notably guanidine, by acting centrally are also capable of eliciting tetany (29). Studies done on tetany in rats have implicated central nervous system involvement because sedative doses of amytal and pentobarbital prevented the onset of attacks and spinal transected rats reacted with the fore-body but not the hind limbs during an attack. In these studies, it was also possible to stimulate tetanic attacks in rats suffering from calcium deficiency or hypoparathyroidism, by a galvanic current or the sound of an air blast.(30). It is of interest that epileptic-like fits have been produced in dogs by injecting small quantities of sodium citrate into the motor cortex or cisterna magna and are presumably due to a decrease in the local concentration of ionized calcium (31). In studies done on respiratory alkalosis in dogs it was found by Seavers et al. that tetany did not occur during anesthesia but did occur in the decerebrate dog and the unanaesthetized dog (32). Likewise the experimental studies on whether or not tonic and clonic spasms are supraspinal in origin or not are contradictory and therefore shed no light on this problem (26).

The fact that hyperventilation is capable of precipitating epileptic seizures would seem to support the idea that its influence on neuromuscular excitability is central. A neurologic mechanism is postulated in the "Munch-Peterson Theory" according to which hyperventilation interupts the autonomous reflexes of the respiratory center causing an irritation of the center which spreads to pathologically altered parts of the brain and thereby precipitates epileptic attacks. To substantiate this, Schultzer and Lebel were able to show that voluntary hypernictation was capable of producing the same symptoms as hyperventilation only in a considerably weakened form (33).

It is therefore difficult to say that hyperventilation tetany is entirely peripheral or entirely central in origin since one finds experimental evidence to substantiate both views. It might well be that hyperventilation tetany is a product of both central and peripheral factors acting synergistically. Such an explanation would bring into harmony the otherwise contradictory findings.

The Role of Calcium

Since hypocalcemia is a known cause of many forms of tetany it would be logical to attribute hyperventilation tetany to it. Yet numerous experiments agree on the fact that with hyperpnea there is no reduction in total serum calcium (3,19,26,33). This in itself, however, does not mean that the role of calcium can be ruled out.

In the early literature the most commonly accepted explanation

for the mechanism of tetany was that of Györgi and others and was based on the assumption that hyperventilation caused a decrease in the serum level of ionic calcium (33). This theory would explain the occurence of tetany, even though total serum calcium remained the same, because it is only the ionized fraction of serum calcium which influences neuromuscular irritability (3,26,33).

If calcium is to be implicated in hyperventilation tetany it is essential that we have a basic understanding of the various fractions of blood calcium and the factors which may influence their concentrations. McLean and Hastings have described serum calcium as existing in two forms, protein bound (non-diffusible) and protein free (diffusible). They state that all or nearly all of the non-protein bound fraction is ionized. Normal values are given as 5 mg./ 100 cc for calcium-proteinate, 4.5 mg./ 100 cc. for ionized non protein bound calcium (normally ranges between 4.25 - 5.25 mg./ 100 cc.), and less than 0.5 mg./ 100 cc. for non-ionized protein free calcium. The latter they identify as calcium citrate. They used a biologic method of assaying ionized calcium, testing the response of a frog heart to the serum being considered. The two factors regulating the level of ionized calcium were found to be the total concentration of serum calcium and the total concentration of serum protein. Clinically, the most important thing is the calcium to protein ratio, since this will determine how much ionized, i.e. physiologically active, calcium is present. When this ratio falls below normal, as happens in hypoparathyroidism, tetany may occur.

Since serum protein level does not change during hyperventilation, if Györgi's thesis is to hold, one must assume that other factors must play a role in altering the level of ionized calcium. Freudenberg and Györgi support this thesis on the basis of the Rona-Takahashi formula which states that in a watery solution, $(Ca^{++})(HCO_3^-)/H^+$ = a constant. Thus with the alkalosis (decreased H^+) of hyperventilation, if bicarbonate remained the same, the calcium ion concentration would necessarily decrease (3,33). There has been considerable objection to this idea because the formula refers to a watery solution and may not be applicable in blood serum (3,33). Then too, evidence has already been cited that bicarbonate level may not remain the same during hyperventilation.

There have been other theories proposed to explain how alkalosis might depress serum ionized calcium. In vitro studies it has been shown that an increase in blood pH causes an increase in the proportion of calcium bound by serum proteins and a decrease in filtrable (protein free) calcium. Brown, however, points out that according to the data of these experiments, a change of pH from 7.4 to 7.7 would cause an ultra-filtrable calcium level of 4.41 mg./ 100 ml., a level higher than that associated with hypocalcemic tetany (3). The majority of in vivo experiments show that hyperventilation does not cause a decrease in the level of dialyzable (protein free) calcium (3,33). Based on the assumption that cerebrospinal fluid calcium reflects the level of diffusible serum

calcium, experiments have been designed to show that with hyperventilation there is a decrease in cerebrospinal fluid calcium. The results of these experiments have been conflicting and the initial assumption that cerebral spinal fluid calcium is determined by the level of filtrable serum calcium has been seriously questioned (3).

There are other factors which may be implicated in a theoretical explanation for a decreased serum ionized calcium. Since potassium and magnesium are higher periodic alkaline salts they would tend to replace calcium and it might be argued that the increased potassium noted in hyperventilation would decrease the ionized calcium (35). There also has been described a calcium-phosphate complex and it has been postulated that increased binding of calcium by phosphate would be the mechanism (35). This has little substantiation since serum phosphate is found to be decreased during hyperventilation and it is said that inorganic phosphate does not combine with ionized calcium at a pH less than ten (36). To assume that ionized calcium might be decreased by a change in the composition and hence binding action of plasma proteins would also be erroneous since no such change has been demonstrated and the iso-electric points of albumen and globulin are low and in the same range and therefore differences in the A/G ratio would not affect materially the binding power of calcium by plasma protein (33,36).

From the above discussion it is evident that there is no generally accepted explanation on how hyperventilation is capable of

decreasing the level of serum ionized calcium. It would seem that those who maintain that such a thing happens have only one recourse, and that is to actually demonstrate a decrease in ionized calcium following hyperventilation. This in itself represents quite a feat since there is no well standardized method for measuring only the ionized fraction of serum calcium. As mentioned before, McLean and Hastings used the method of bioassay (frog heart) but one might question the specificity and quantitative sensitivity of such a method. With the frog heart method, there was no detectable decrease in ionized calcium when the pH of the perfusing fluid was increased from 7.35 to 7.60 (3).

In the Scandinavian literature there is a report on the determination of ionized serum calcium based on the solubility of calcium iodate. Details are not given as to the exact analytic procedure but with their method the authors found no significant reduction in ionized calcium during hyperventilation tetany (33). As can be readily understood from the foregoing discussion, methods designed to separate the diffusible from the non-diffusible fractions of serum calcium are of no aid since not all of the diffusible fraction is necessarily ionized.

In an attempt to find an analytic method for determining ionized calcium this author considered a procedure described by Drevon and others in the recent French literature (37). This method makes use of the compound ethylene diamine tetra-acetic acid

(EDTA) and murexide (ammonium purpurate). In the presence of calcium, the indicator murexide, normally violet in color, takes on an orange color characterizing the formation of a calcium - murexide complex. If one then adds to this medium a standardized solution of the sodium salt of EDTA, the calcium enters into a new combination with the latter reagent and when the theoretical quantity has been added, the original violet color of murexide reappears. Since the volume of standardized EDTA solution necessary to return the indicator to its original color is in direct proportion to the amount of calcium in the medium, one can calculate from this volume the amount of calcium present. Employing this principle, the authors have devised a microdetermination procedure, using a spectrophotometer to detect the color change. This would appear to be a method applicable to our studies if it were not for one deleterious factor. Unfortunately, the reaction between EDTA and calcium apparently takes place only in a medium having a pH of 12. Therefore all samples to be studied first must have their pH's raised to 12 by adding sodium hydroxide. This in itself would probably change the level of ionized calcium and therefore obscure the original concentrations in the samples.

It is hoped that this procedure will be perfected so that it may be used to give a valid <u>direct</u> measurement of ionized calcium at the true pH of a blood sample.

Various investigators have attempted to discover by <u>indirect</u>

methods whether or not ionized calcium is a factor. These studies are based on the therapeutic effect of calcium chloride and assume that it will raise blood ionized calcium and therefore be therapeutic if a deficiency of ionized calcium is the etiologic factor. Engel et al. found that administered calcium chloride had no significant effect on EEG slowing, but did reduce tingling during hyperventilation in two subjects (1). Donovan found it to be effective in one case and Harwood states that it is capable of aborting an attack (38,39). On the other hand Schultzer and Lebel, by their previously mentioned method of measuring ionized calcium, found that calcium chloride failed to prevent tetany even though it raised the level of ionized calcium above normal concentration (33).

In summary, from the bulk of evidence it would appear that a deficiency of ionized calcium is not the basis for hyperventilation tetany. However, most of the evidence is indirect and not entirely conclusive. It will probably not be conclusive until a sensitive method is devised for measuring directly the concentration of serum ionized calcium and a large enough group of subjects are studied.

Other Cations

It is quite possible that there are cations other than calcium which play a role in hyperventilation tetany. One of these may be magnesium. Rats and dogs on a diet deficient in magnesium show vasodilatation, hyper-irritability, tonic and clonic convulsions, and tetany (26,30,40,41). It is likely that there is a physiologic

antagonism between magnesium and calcium because with deprivation of both one does not see the rapidly moving and fatal tetany characteristic of only a magnesium deficiency (42). As yet there is little clinical evidence that magnesium deficiency occurs in man, nor have there been adequate studies in which serum magnesium levels were measured during hyperventilation. In one study Kerr found no significant change in serum magnesium in patients with hyperventilation tetany (2). Certainly there is a paucity of data on this subject and it bears further investigation.

It is quite possible that the tetany of hyperventilation is due to a disturbance in the normal balance between several electrolytes. We know that in addition to calcium and magnesium, changes in sodium and potassium concentration also affect responses of the neuromuscular system (26). Neuromuscular irritability, no doubt, depends on the interplay between several factors. The following formula has been suggested by Cantarow to express these relationships (43).

Neuromuscular Irritability is proportional to:

$$\frac{[Na^+] + [K^+]}{[Ca^{++}][Mg^{++}][H^+]}$$

According to this scheme, the well documented increase in potassium concentration and decrease in hydrogen ion concentration occuring during hyperventilation would contribute to increased neuromuscular irritability. Perhaps this is augmented by a decrease in calcium

and magnesium ions, though as yet, we have no proof of these changes. The only apposing factor would be the observed fall in sodium, but perhaps this is more than compensated for by the previously mentioned changes.

Adrenalin and Tetany

In addition to those already discussed, data from various studies indicate that still other factors may play a role in hyperventilation tetany. We have already mentioned the fact that adrenalin may be one of these. Adrenalin is known to increase the summation of nerve impulses and to act as a cerebral cortical stimulant (2). In addition, one study has shown that normal children after five to six minutes of hyperventilation could be rendered tetanic by intravenous adrenalin without further hyperventilation (25). Harvey and Lilienthal believe that this is due to a peripheral action of adrenalin and in further support of this idea have shown that hyperventilation tetany does not occur in the hand to which circulation has been occluded prior to the onset of hyperventilation, and the Trousseau phenomenon develops in the hand of a patient with latent tetany even though the motor nerves to that hand have been blocked with procaine (25). They have also demonstrated that the intra-arterial injection of Adrenalin in patients having hypocalcemia due to hypoparathyroidism evoked immediate and LOCAL TETANY. Since the vasoconstrictor effect of the adrenalin persisted longer than did tetany, one can not attribute this effect to vasoconstriction. Because adrenalin affects the migration of potassium ions, they believe that adrenalin's tetanic action is

best attributed to an altered potassium to calcium ratio. (Both cations have an antagonistic effect on tissue irritability). Whether or not similar changes occur during hyperventilation tetany is not clearly shown from their experiments (25). It may well be that the outpouring of adrenalin which accompanies the stress of hyperventilation, albeit not the only factor, potentiates tetany.

Hypoglycemia

Hypoglycemia is another factor which may influence tetany. In discussing this subject, Brown quotes reports which associate the two and notes that hyperventilation is said to decrease the hyperglycemic effect of adrenalin. He also indicates, however, that other studies fail to demonstrate hypoglycemia in association with hyperventilation (3). The latter is consistent with a statement by Rapoport that blood sugar does not change in a uniform way during hyperventilation (19). Any relation between blood glucose and hyperventilation tetany is therefore highly questionable.

Tetany And Blood pH

There is no doubt about the fact that hyperventilation causes a rise in blood pH, but there is doubt as to whether or not the latter in itself can cause tetany. Descriptions of gastric tetany, presumably due to the loss of hydrochloric acid and consequent alkalosis, as well as descriptions of bicarbonate tetany, due to the excessive ingestion of sodium bicarbonate, would seem to

verify the fact that alkalosis alone can cause tetany (2)(26). On the other hand, there has been no experimental production of tetany by merely elevating blood pH and it has been shown that when arterial carbon dioxide is reduced to one-half its normal value tetany follows regardless of what blood pH is (3). Short also agrees that tetany is related to arterial CO_2 tension rather than blood pH (24). This is of importance clinically because if such is true, then acidifying agents (NH_4Cl) have no place in the treatment of hyperventilation tetany and should be replaced by methods used to increase the concentration of arterial carbon dioxide tension, i.e.,having the patient hold his breath, re-breathe from a bag, or breathe from a supply of carbon dioxide.

Hypoxia

The one remaining factor relevant to a discussion of tetany is tissue hypoxia (2). There are several previously mentioned circulatory changes during hyperventilation all of which can contribute to hypoxia. These include vaso-constriction, inhibition of oxyhemoglobin dissociation, and circulatory impairment due to a decreased venous return. The Trousseau phenomenon suggests that vascular insuffieiency and hypoxia potentiate tetany but again our evidence is inconclusive.

Summary on mechanism of tetany

From the foregoing discussion, it is evident that there is

more than one factor capable of potentiating tetany during hyperventilation. It is the opinion of this writer that the mechanism by which hyperventilation causes tetany is due to the summated effect of several factors, each in itself known to increase neuromuscular irritability. These changes are due to perpheral as well as central influences and they include an increase in arterial blood carbon dioxide, an alteration in the relative concentrations of certain electrolytes: hydrogen ions, potassium ions, ionized calcium, and perhaps magnesium; a condition of tissue hypoxia, an increased secretion of adrenalin, and possibly the presence of hypoglycemia.

D. Localized Muscle Spasm

The localized pains which afflict patients having the hyperventilation syndrome are due to spasm of a specific muscle or group of muscles. Such spasm is capable of producing the common symptoms of abdominal, back, or precordial pain.

Wolf has done a fascinating study which reveals how a number of symptoms may be caused by diaphragmatic spasm. He chose seventeen subjects all of whom were quite anxious and complained of inability to get a full breath. While fluoroscoping these people he purposely induced a good deal of anxiety in them and found that inspiration became jerky. In addition, the inspiratory excursion exceeded the expiratory so that the diaphragm assumed a progressively

lower and lower position to the point where there was a sustained diaphragmatic contraction.. At this point, the subject became dyspneic and complained of being unable to take a full breath. Other things noted were pain in the precordium, chest, or shoulder, pallor, sweating, a fall in blood pressure, and dysphagia. The latter symptom Wolf attributes to occlusion of the cardiac end of the esophagus by diaphragmatic spasm (44).

One can only postulate on the mechanism of localized muscle spasm. It is most likely related to the same factors increasing neuromuscular irritability which we discussed under the subject of tetany. However, one is at a loss to explain why these factors become manifest only in a specific area.

Wolf's experiment suggests that diaphragmatic spasm is due to an incoordination of the normal respiratory mechanism, perhaps secondary to a disruption of normal reflex mechanisms. We have mentioned the fact that hyperventilators tend to use their accessory muscles of respiration and one might postulate that chronic tension in these muscles is the basis for pains in the neck, shoulders, and thoracic region.

E. Respiratory Symptoms

We have already discussed the fact that these patients have an incoordination of their respiratory mechanics so that clinically we find them making excessive use of their accessory muscles, in a peculiar heaving type of respiration, with sighing, and yawning.

Their paradoxial complaint of dyspnea despite hyperventilation is perhaps due to the previously mentioned relatively immobile and contracted diaphragm.

F. Cardiac Symptoms

Complaints of precordial pain and dyspnea are mistakenly referred to the heart. Actually they are related to spasm of the diaphragm or intercostal muscles. Gaseous distention of the stomach with pressure on the diaphragm may also be the basis for these symptoms. The palpitations noted are perhaps due to the decreased venous return said to accompany hyperventilation, which would cause compensatory tachycardia. It is doubtful that the ECG changes mentioned give rise to any symptoms. Likewise blood pressure and cardiac output are maintained and therefore should not be incriminated.

G. Gastrointestinal Symptoms

The complaint of dryness of the throat is easily related to the increased ventilation with evaporation of moisture from the mucous membranes. Bloating, belching and flatulence are due to the aerophagia which accompanies hyperventilation, and one can frequently elicit a tympanitic note over the left upper abdominal quadrant (6). Then too, sympathetic stimulation accompanying the stress of hyperventilation may well cause a contraction of the sphincters of the gastrointestinal tract and promote further distention. As discussed above, dysphagia may be related to diaphragmatic spasm with occlusion of the cardiac end of the esophagus.

H. Psychic Components

Nonspecific symptoms attending the hyperventilation syndrome of easy fatigue, weakness, insomnia, and chronic exhaustion may in part be due to the continual increased expenditure of energy in the work of hyperventilating. For the most part, however, these are probably only manifestations of chronic anxiety and tension.

Psychic components of the syndrome such as persistent anxiety, tension, apprehension, and hypochondriasis are to be thought of more as causative factors than as secondary manifestations. There is no doubt, however, that the multitude of symptoms arising from hyperventilation can serve to increase the patient's anxiety level and maintain the process even after the original stressful situation has been resolved. In such patients, simply demonstrating to them how their hyperventilating causes the complete symptom pattern of which they complain may afford the reassurance and insight necessary for breaking the cycle.

INHERENT DIFFERENCES BETWEEN HYPERVENTILATORS AND NORMALS

In all of the foregoing discussion the physiologic changes mentioned would happen to any of us if we hyperventilated for a long enough period of time. One of the striking things which identify the patient having a true hyperventilation syndrome is the fact that hyperventilation for a very short period of time, as little as thirty seconds, will precipitate symptoms whose development in a normal person would require several minutes of hyperventilation. This suggests the concept that even when at rest there is derangement of the hyperventilator's physiology which makes him more sensitive to overbreathing than the normal person. So far, we are only able to theorize as to what this difference is.

It has been suggested that hyperventilation affects anxious people more than those doing it voluntarily because the former have synergistic effects from cortical and other organ stimulation (2). The person who hyperventilates as part of an emotional disorder would be expected to have concomitant reactions to stress in other systems. We have already referred to the fact that sympathetic nervous system stimulation, the outpouring of adrenalin, and cortical stimulation are all capable of potentiating the various effects of hyperventilation. One might assume that the individual who hyperventilates voluntarily as an experimental subject does not experience the latter equivalents of stress and therefore is less sensitive to hyperventilation.

Previous reference has been made to the vasoconstrictor response to carbon dioxide deficit as a homeostatic mechanism for cerebral tissue. Gibbs has demonstrated that in some normals and in patients with petit mal epilepsy there is a relative incompetance of this mechanism so that slow waves can be produced in the EEG with only minimal hyperpnea (9). We might postulate that such a cerebral homeostatic defect is present in patients with the hyperventilation syndrome. As yet there is no experimental evidence which would bear out this hypothesis but certainly it would be worthwhile to study a group of these patients in terms of how effective their cerebral vasoconstriction is in response to a carbon dioxide deficit.

Another hypothesis lies in the concept of subclinical alkalosis. It has been shown that in patients with pre-existing alkalosis from causes such as vomiting or excessive alkaline treatment, only moderate hyperventilation is required to produce symptoms of severe tetany (7). It may be that the hyperventilator, even when at rest, is in a state of sublinical alkalosis and that only mild hyperventilation quickly puts him past the threshold of alkalosis at which symptoms occur. Such a state of mild alkalosis could be explained by assuming that because of their chronically tense personalities, these individuals are hyperventilating moderately almost all of the time. It is only at times when they are under relatively severe stress and are hyperventilating vigorously, that their symptoms become manifest; and then, they develop very readily. Here too, experimental data is lacking and it would be of value to compare the blood pH of a group of

known hyperventilators and a group of normals under "basal" conditions when they are not specifically told to hyperventilate and then after each group has hyperventilated for equal periods of time.

Another hypothesis which would account for the increased sensitivity of "hyperventilators" to hyperpnea involves the role of blood electrolytes. One might assume that in these individuals there is a constitutional or aquired abnormality in the metabolism of certain electrolytes. This would be reflected in a less than normal buffering capacity for small changes in blood CO_2 or could in itself potentiate the electrolyte imbalances occuring during hyperventilation. We have already mentioned some of the body's compensatory mechanisms for meeting prolonged hyperventilation alkalosis. One of these involves renal excretion of free alkali and it may be that this compensatory mechanism is impaired in patients having the syndrome. On the other hand, a depletion of body sodium due to chronic hyperventilation may also have some deleterious influence. One can only speculate about these changes since experimental data is lacking.

It would certainly be of interest to study urinary excretion of at least sodium, potassium, and magnesium before and after hyperventilation in normals and in hyperventilators to see if there is any difference in response between these two groups. Such studies were done on urine sodium and potassium by this author on two patients demonstrating the hyperventilation syndrome and are described in the Appendix of this paper. The results of this were inconclusive and further investigation is necessary. Similar studies are

now being done by Drs. Musser and Gordon of the University of Wisconsin Medical School.

Because of the possible differences between electrolyte metabolism in normals and in hyperventilators one wonders whether or not adrenal cortical activity might be a significant factor.

In the recent literature there are reports on a new clinical syndrome, "primary aldosteronism" (45,46,47). It is of interest to this discussion because those cases reported have many symptoms similar to those one finds in hyperventilation. These include intermittent tetany, paresthesias, periodic severe muscular weakness and paralyses, and nervousness. Other characteristics of the disease not usually a part of the hyperventilation syndrome are polyuria, polydipsia, hypertension and edema.

In the urine of these patients one finds an abnormally high concentration of aldosterone. The latter appears to be the active principle of the amorphous fraction of adrenal cortical extract. It has been crystallized and its formula has been established. It is the salt retaining steroid of the adrenal gland and probably the main endocrine agent for the regulation of sodium, potassium, chloride and perhaps magnesium metabolism. An abnormally high concentration has been found in the urine of patients having cardiac failure, decompensated hepatic cirrhosis, nephrotic edema, and experimentally produced prolonged sweating while on a low salt diet. The latter conditions have been termed "secondary aldosteronism".

Studies on patients with primary aldosteronism demonstrate

below normal plasma levels of potassium, magnesium, calcium, and chloride. Plasma sodium is increased as is bicarbonate and the pH is elevated. These patients have a tremendous capacity for retaining sodium and excreting potassium. The cause of this syndrome is not clear but it appears to be an adrenal cortical hyperfunction and in one reported case, an adrenal cortical tumor was found.

Though this syndrome has features in common with the hyperventilation syndrome - mainly tetany, paresthesias, nervousness, and alkalosis they are much unlike each other in many ways. In hyperventilation we see a decrease in plasma sodium and bicarbonate and an increase in plasma chloride and potassium; total calcium remains unchanged and magnesium has not been adequately assessed. Most of these electrolyte changes are opposite to what we see in primary aldosteronism. However, because of some of the similar clinical features of these two syndromes, investigation into the role of aldosterone in hyperventilation might prove fruitful.

SUMMARY

1. Though it has numerous organic causes, hyperventilation is most commonly seen as a manifestation of chronic stress, tension, or anxiety.

2. The major symptoms and signs of the hyperventilation syndrome are of two types:

1) A reduction in the level of consciousness

2) Increased neuromuscular irritability.

There are also numerous minor non-specific manifestations. The most common symptom is peripheral paresthesia, the most common sign is disordered breathing, and tetany occurs only rarely.

3. Hyperventilation causes physiologic changes in almost every organ system of the body.

A. Respiratory

1) Decreased alveolar CO_2 tension

2) Impairment of normal respiratory control mechanism.

3) Use of accessory muscles of respiration and an immobile diaphragm

B. Cerebral

1) Cerebral vasoconstriction and EEG slowing due to a decreased arterial CO_2 tension.

C. Cardiovascular

1) Vasoconstriction in cerebral and skin arterioles

Vasodilatation in splanchnics and major arterioles of the extremities.

2) Cardiac output and blood pressure remain the same.

3) Venous return is impaired.

4) ECG - Inversion of T wave and depression of S-T Segment.

5) Decreased HbO_2 dissociation.

D. Blood Chemistry - These changes are summarized in the chart on page 25.

E. Endocrine - Increased secretion of adrenalin and possibly adrenal cortical hormones.

F. Neuromuscular - Increased irritability.

G. Gastrointestinal and Urinary - Decreased gastric HCl secretion and contraction of sphincters.

4. The author has attempted to correlate the clinical picture with the above physiologic changes.

A. Reduced consciousness is related to decreased CO_2 tension in cerebral tissues and possibly cerebral hypoxia.

B. Paresthesias - are most likely due to peripheral hypoxia.

C. Tetany in hyperventilation is due to the summated effect of several factors which include peripheral and central influences, electrolyte imbalance, hypoxia, and adrenalin. The role of ionized calcium is still debatable, there being as yet no method of measuring serum ionized calcium.

(The general subject of tetany has been discussed in detail).

D. Localized pains are due to muscle spasm. The latter probably having the same origin as tetany. The diaphragm, intercostals, and accessory muscles of respiration are most commonly involved.

E. Gastric dilatation and diaphragmatic spasm give rise to dyspnea, precordial pain, dysphagia and abdominal distention.

F. Many of the symptoms noted are merely direct manifestations of stress, tension and anxiety. Sympathetic nervous stimulation plays an important role.

5. There are gross differences in the response to hyperpnea between normal persons hyperventilating voluntarily and individuals having the hyperventilation syndrome. The author has presented several hypotheses, none of them proven, to explain these differences.

Perhaps the true hyperventilator has:

A. A greater number of synergistic responses to hyperventilation and emotional trauma.

B. A defect in the cerebral vasoconstrictor response to decreased CO_2 tension.

C. A constant state of subclinical alkalosis.

D. A defect in electrolyte metabolism - perhaps on the basis of abnormal adrenal cortical activity.

6. Case histories and preliminary experimental studies are presented in the Appendix.

APPENDIX

CASE I

The following is a presentation of a case of the hyperventilation syndrome in which ECG changes were noted and blood pH studies done.

C.B.S. is a forty-three year old male truck driver who during a routine chest film in July, 1954, was discovered to have nodular infiltrative disease involving both lung apices which was subsequently diagnosed as tuberculosis. He was seen by the author while undergoing treatment at the VA Hospital in Madison, Wisconsin.

When seen on February 1, 1955 he gave a three year history of intermittent episodes of weakness, dizziness, light headedness, sweating and heavy breathing. These were frequently, but not always, related to heavy exertion. At no time has he had ankle edema, significant precordial pain, or progressive exertional dyspnea.

It is interesting that in October 1954 he was seen at the VA Research Hospital in Chicago, Illinois, because of symptoms of shortness of breath, anxiety, and moderate hypertension. He presented no evidence of congestive failure: lung bases were clear, venous pressure was normal, there was no peripheral edema, blood pressure was 176/135 and pulse was 130/minute and strong.

His work up at the VA hospital at Madison in December, 1954 was negative for significant cardiovascular disease. On x-ray, the cardiac silhouette was normal. His blood pressure was 125/110, yet

kidney studies including IVP, PSP, urea clearance, and routine urinalysis were within normal limits. Regitine test and a provacative histamine test were also negative. Routine admission and progress ECG's were normal except for the fact that he demonstrated a positive hyperventilation test with inversion of the precordial T waves.

Within one minute of hyperventilation the patient noted symptoms of lightheadedness, blurred vision, a sensation of floating, dyspnea and suffocation. He became warm and sweated profusely but showed no signs of latent or manifest tetany. He volunteered that he felt the same at this time as he felt during past described episodes.

Because of the classical clinical picture and electrocardiographic changes which this patient demonstrated it was of interest to correlate these with changes in blood pH. It was found that at rest he had an arterial blood pH of 7.38. Following two minutes of hyperventilation, at which time the patient noted the above described symptoms, his arterial blood pH had risen to 7.54. The details of this experiment are discussed below.

DISCUSSION: The determination of arterial blood pH involves several variables all of which must be accurately taken into account if valid results are to be obtained. The temperature of the blood and the electrode must be constant and equal because temperature changes have a profound effect on blood pH, pH rising with a fall in temperature. The duration between the time the sample is withdrawn and the time it is read is important because following removal from the body, blood

pH falls with the passage of time. This is in part due to continuing glycolysis and accumulation of lactic acid. Lowering the temperature will inhibit glycolysis. Exchange between the blood sample and the atmosphere must be prevented because a loss of carbon dioxide to the atmosphere will increase blood pH, whereas an increased amount of oxyhemoglobin, as would occur if an unsatured blood sample were to take up oxygen, will lower the pH. The method of pH determination used in this experiment is essentially that recommended by the studies of Russell H. Wilson and is designed to minimize the variables of temperature, time, and gas exposure(48).

METHOD: An instrument which was specifically equipped at the VA Hospital of Madison for measuring blood pH was used. It consists of a Cambridge pH meter and a constant temperature cabinet kept at 37°C. The working entrances to the cabinet are covered by a pliable plastic material and the glass electrode assembly with its blood chamber as well as the buffer solutions, are housed within the cabinet. Thus blood sample, electrode, and buffers are all maintained at the same temperature. Two commercially prepared buffers having pH's of 6.96 and 7.40 are used to standardize the instrument. The meter itself has an accuracy of $\pm$ 0.02.

Syringes were prepared by placing a drop of mineral oil on the plunger of the syringe before inserting it in the barrel thus assuring anaerobic conditions. Then 2 cc. of heparin were drawn up into the syringe and all except that which adhered was dispensed.

Skin at the injection site was prepared by the local infiltra-

tion of procaine and 10 cc. of blood were withdrawn from the femoral artery. The first sample was drawn when the patient was at rest, breathing quietly, and asymptomatic. The second was drawn after he had hyperventilated in the recumbent position for two minutes and had the aforementioned symptoms. Readings were made on the whole blood samples one minute following their withdrawal from the body.

CASE II

I.B. is a thirty year old woman who eight months prior to admission to the University of Wisconsin Hospitals had a sudden attack of momentary unconsciousness followed by crushing precordial pain and palpitation which lasted for three hours. She remained at bed rest for the next three days and during that time had severe occipital headaches, weakness, dizziness, and general malaise. In the following eight months she had three similar episodes.

A review of systems revealed frequent headaches since childhood, tinnitus, increased salivation and dysphagia. She stated that she slept poorly and volunteered, "I have been nervous all of my life".

I.B. was born in Latvia but at the age of fourteen her father, who was a banker and feared the Russians, fled with his family to Germany. There, in 1950, she was married to her present husband who was an American soldier stationed in Europe. They now live in a small community in Wisconsin where her husband works as a recruiting officer.

In interviewing her it was frankly apparent that she was a

tense, politely hostile, domineering individual with a meticulous and compulsive pattern of personal habits. In her perfectionistic demands she found herself dissatisfied with her husband's modest social and economic position. She freely admitted that she thought of him as a weak individual subject to her complete domination. In addition she expressed deep resentment towards her three and one-half year old son who restricted her self-directed activities.

Physical examination was essentially negative. Routine blood and urine studies were within normal limits, as was cardiac fluoroscopy.

Her electrocardiogram showed low T waves in leads I,II,III, AVR, AVF, V-5, and V-6. During hyperventilation the T wave in lead II completely disappeared, reappearing when breathing returned to normal. The ECG was otherwise normal.

Within one minute of hyperventilation she noted dizziness, numbness and tingling of the ears, hands, and periorbital region, and a sense of weakness and paralysis in her hands. Following two minutes of hyperventilation frank carpopedal spasm was evident and the patient complained that voices were distant and she had difficulty speaking. No pain was noted. When instructed to hold her breath, these symptoms quickly disappeared.

Urine sodium and potassium studies on this patient are discussed later. In these studies she hyperventilated for two minutes; displaying the signs and symptoms noted above.

CASE III

C.B. This thirty-nine year old man entered the University of

Wisconsin Hospitals with a chief complaint of dizziness. His first episode occurred two weeks prior to admission and was associated with a feeling of generalized weakness. After that he had three more attacks which were so severe that he was unable to continue work. All four episodes occurred while the patient was at work and they happened on a Tuesday or Thursday. It was later revealed that he was enrolled in a course in radio servicing which met on these nights.

He had numerous other somatic complaints. Headaches frequently afflicted him. These arose from multiple sites and would begin as a dull aching sensation, ultimately localizing as a sharp stabbing sensation in the right temporal region. He noted frequent precordial pains associated with a sense of gastric distention. These were aggravated by greasy or spicy foods. "Changes in the weather" caused him to vomit. He also had vague pains and stiffness in the wrists, thighs and hips.

Past history revealed that in 1943 he was treated medically for a duodenal ulcer (confirmed by x-ray). In 1949 he was seen at the Mayo Clinic for multiple joint and head pains but no organic disease could be found.

In interviews with the patient it was learned that he has worked as an assembler in a furniture factory for the past fourteen years and that for the past twelve years he has served as the union steward. The latter position was a recurring source of anxiety. In his mediating disputes between a fellow worker and management, the patient became very personally involved in the arguments and often came away from them with severe headaches and palpitation. He found these

disputes too complex and personally taxing but because of a strong sense of responsibility he was unable to resign as steward. Disappointment with his own career made him feel inferior to his two brothers who were successful businessmen. Through his night school course, he had hopes of advancing himself and yet he feared that much of the technical detail of the course was beyond his comprehension.

In his general personality he revealed himself to be a person who is unusually sensitive to criticism, continually demanding approval from others, and avoiding intimate social relations. At the time he was seen as a patient he had built up a good deal of anxiety over his course in radio servicing; apparently feeling that this was his one chance to really prove himself and yet fearfully aware of the fact that he might not make the grade.

Physical examination was essentially negative and urinalysis and routine blood count were unremarkable. An electroencephalogram was normal and revealed no change with hyperventilation.

Hyperventilation for one minute caused him to complain of dizziness, lightheadedness, a frontal headache, and numbness of the hands. None of the signs of tetany were present. The patient admitted that these symptoms were comparable to those he noted in the past and also stated that he was aware of the fact that at those times his breathing was unusually heavy.

Urinary sodium and potassium excretion studies were done on this patient and will be discussed later. In this study he hyperventilated for four minutes at which time in addition to the above

symptoms he noted tingling of the fingers and sharp pains at the angles of the mandible and a positive Trouseau was elicited.

Sodium and Potassium excretion studies

Procedure:

1. The subject is instructed to have nothing to eat from midnight preceding the day of the experiment, until the termination of the experiment. He is to be at bed rest during the course of the experiment.

2. At 7 A.M. he empties his bladder completely, discarding the urine. He drinks two and one-half glasses of water so as to have an adequate volume of urinary excretion.

3. At 8 A.M. he empties his bladder completely and all of this urine is collected as sample one.

4. At 9 A.M. he does the same, this being sample two. He then hyperventilates vigorously for from two to five minutes, depending on the patient's ability and cooperation. Signs and symptoms are carefully noted.

5. At 10 A.M. he again empties his bladder completely and this is collected as sample three.

6. The last specimen is taken at 11 A.M., sample four.

Analyses

The above four specimens are each analyzed on a flame spectrophotometer for urinary sodium and potassium and the results are expressed as total milliequivalents excreted per minute.

Results

These are presented for the two patients C.B. and I.B., whose histories we have already discussed. The symptoms and signs which they experienced during the experiment are noted in their respective histories.

I.B.

	Urine Sodium (total mEq./min)	Urine Potassium (total mEq./min)
Urine Sample 1	0.037	0.024
Urine Sample 2	0.029	0.023
Hyperventilation for two minutes		
Urine Sample 3	0.039	0.023
Urine Sample 4	0.029	0.025

C.B.

Urine Sample 1	0.063	0.048
Urine Sample 2	0.029	0.030
Hyperventilation for four minutes		
Urine Sample 3	0.038	0.020
Urine Sample 4	0.032	0.022

Discussion

From the data on these two patients alone, it is evident that no conclusions can be drawn as to the effect of hyperventilation, in subjects known to have the hyperventilation syndrome, on urinary sodium and potassium excretion. It is interesting to note that in both cases there was a rise in urinary excretion of sodium in the sample collected after hyperventilation (compare urine sodiums for samples two and three in each patient). It is questionable how much significance can be attached to this, however, since there are variations of an equal or greater magnitude between the two control samples (compare urine sodiums for samples one and two in each patient).

We are at a loss to explain the latter variation and only further studies will reveal its cause. Perhaps even during the collection of specimens one and two the subjects, who were supposedly breathing normally, were actually, at times, voluntarily hyperventilating, thus offsetting the comparison between excretions at rest and following hyperventilation.

The studies on these two subjects are, at best, only preliminary ones, and many more subjects should be studied. It is hoped that a more valid method will be worked out by which differences in electrolyte excretion between normal subjects hyperventilating and patients having the hyperventilation syndrome will be brought out.

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