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## SIGNS AND SYMPTOMS OF ELECTROLYTE DISORDERS†

> A genuine understanding of the functions of sodium, potassium, cal-
> cium, magnesium and their salts in the organism would necessitate a
> comprehension of the nature of protoplasm and its behaviour in living
> cells, something we have not begun to attain.
>
> J. P. Peters and D. D. Van Slyke:
> Quantitative Clinical Chemistry, 1931.

Since Peters and Van Slyke published their classic text there has been an enormous increase in understanding of the processes governing the transport of ions across cell membranes. It is chastening, nevertheless, to reflect that the major clinical manifestations of electrolyte disorders observed at the bedside by history, physical examination, and bedside laboratory apparatus were known well to clinicians 40 and more years ago.

For the most part, disturbances of the distribution and concentration of body electrolytes affect cellular function rather than structure. Exceptions to this rule are seen in the nephropathy and myocarditis of severe potassium deficiency and in the well-marked lesions of calcium intoxication, but the predominant effect of alterations in electrolyte concentration are likely to be detected in their influence on chemical and electrical gradients across cell membranes. Hence the symptomatology of electrolyte disorders has much to do with changes in the behavior of excitable tissues. Neurological disturbances are prominent, as are changes in cardiovascular function and in skeletal muscle. Most important of all from the standpoint of the clinician is that most of the symptoms described in this review are reversible with proper therapy.

### HYPERNATREMIA

The sense of thirst is so strong a defender of the serum sodium in normal individuals that hypernatremia is never encountered unless thirst is impaired or rendered ineffective because the patient is comatose or is denied access to water. Even in patients with diabetes insipidus in whom water losses may amount to gallons per day, the intake of water usually keeps pace with its excretion. Serum sodium is elevated minimally or not at all as long as the patient is awake and able to drink. When thirst is no longer permitted to operate, however, the serum sodium rises. Hypernatremia is especially

likely to become a problem when water losses are enhanced. It is commonly seen under the following circumstances:

1. *After the dessication of a semi-comatose patient.* A good example is the elderly patient who has a stroke and is unable to drink normally. After a week of lethargy and gradually decreasing responsiveness, complicated during the last few days by a low-grade fever, she is admitted from the nursing home to a general hospital. The serum sodium is found to be 165 m Eq/L.

2. *When urinary losses of water are greatly increased as a result of restricted intake.* Examples include neurosurgical patients with diabetes insipidus occurring post-operatively, other patients in whom high protein feedings are dissolved in minimal amounts of water and fed by stomach tube so as to produce a large urea diuresis, and patients with diabetes mellitus in whom prolonged glucose diuresis has resulted in losses of water that exceed those of salts. Some of the most striking instances of hypertonicity we have seen have been in patients in whom relief of urinary obstruction has resulted in the sudden diuresis of large volumes of dilute urine which could not be adequately replaced by mouth because the patient was comatose or lethargic.

3. *Where there are large evaporative losses from the skin.* When the normal vapor barrier of the skin is destroyed by extensive second and third degree burns and especially when the burns are treated by the "open method," hypernatremia commonly ensues.

4. *After salt poisoning.* A greatly increased intake of salt in a constant inadequate volume of water may produce severe hypernatremia, as described in the infants seen by Finberg and his collaborators.[1]

5. *As a result of peritoneal dialysis with hypertonic glucose solutions.*[2]

6. *In patients in whom the sense of thirst has been selectively depressed or eliminated.* In all of these cases neurons of the thirst center in the hypothalamus presumably have been damaged or destroyed. The most common cause is a cerebral tumor, such as a glioma, a craniopharyngioma, a pinealoma or a metastatic tumor,[3] but a similar syndrome has been reported in patients with poliomyelitis of the bulbar type and in those with meningitis. In some patients, like the microcephalic and mentally retarded boy with hypernatremia described by Segar,[4] a specific neurological diagnosis is difficult to define. "Resetting of the osmoreceptors" has been invoked frequently as a possible explanation of chronic hypernatremia, but destruction of the thirst center seems a more plausible explanation. In the single case reported by Segar[4] the threshold for water diuresis appeared elevated, from a serum sodium concentration of 140 m Eq/L. to 153 m Eq/L., thus providing evidence for "resetting" of the osmoreceptors governing the release of antidiuretic hormone.

The most important symptoms and signs associated with hypernatremia are referrable to the *nervous system*; indeed, it is sometimes difficult to decide whether neurological signs are a result of the hypertonicity or of the primary disease. The degree of neurological disturbance appears related roughly to the rate at which hypernatremia has appeared. A reason for this is apparent when one considers the pathology of the brain in experimental hypertonicity in animals. If severe hypernatremia is rapidly induced in kit-

tens by the injection of hypertonic saline, the sudden shrinkage of the brain tears dural blood vessels, producing cerebral hemorrhages and subdural hematomas.[5] When hypertonicity is produced more gradually, however, cerebral hemorrhages are not seen and functional changes are less pronounced. Thus, an occasional patient has been reported whose consciousness appeared unimpaired with serum sodium as high as 170-180 m Eq/L. There is some evidence that the intracellular solute content of brain tissue increases in chronic hypernatremia so that cellular volume can be better preserved.[6]

The earliest effect of hypernatremia usually is depression of the central nervous system producing lethargy that progresses to coma. In children signs of irritability are usual and a high-pitched cry is heard,[7] similar to that characteristic of meningitis. The reflexes are sometimes hyperactive, but are usually normal. Muscle rigidity and tremor may occur. Hyperreflexia may be marked and spasticity may be present; in such cases cerebral bleeding may contribute to the picture. Epileptiform seizures may occur. Paradoxically, these are sometimes exaggerated when the level of serum sodium is brought down to normal by the administration of water.[8] Convulsions are probably best explained by focal hemorrhages in the brain, but they may also find an analogy in the fact that when concentrated solutions of sodium salts are injected locally over the cortex of the brain, seizure activity is evoked.[9] Such activity, interestingly enough, is not elicited by hypertonic solutions of mannitol.

As might be expected, the cerebrospinal fluid protein frequently is elevated and the electroencephalogram is often abnormal. Abnormalities specifically due to hypernatremia are often difficult to define in patients because of the frequent clinical association of other cerebral lesions, which themselves contribute to the development and maintenance of high serum sodium. In rabbits in which hypernatremia has been induced experimentally, the electroencephalogram shows a generalized reduction in voltage, disappearance of fast activity, and bursts of 4 to 5 per second spindle-like activity, progressing to high voltage waves at a frequency of 1-3 per second.[10]

Permanent brain damage may result from severe hypernatremia, especially in children. Spasticity, seizures, and retardation of growth and mental development have all been recorded. For example, persistent neurological abnormalities were present in one third of 32 children examined one to five years after an episode of hypernatremia associated with dehydration.[11] It seems likely that these are the late effects of subdural effusions, subarachnoid hemorrhages, and intracerebral bleeding.

The symptom of muscular weakness usually is overshadowed by disorientation and coma, but in occasional patients with chronic hypernatremia it may dominate the clinical picture. A patient with an optic glioma that had produced diabetes insipidus as well as loss of thirst, found quadriceps weakness the most disabling symptom as well as the most reliable in predicting hypernatremia. He was unable to mount the stairs when his serum sodium was 170 m Eq/L. but promptly gained strength to climb normally when enough water was administered to reduce serum sodium to normal levels.

While hypernatremia *per se* does not appear to damage renal function, the loss of body water that usually accompanies it is reflected in moderate

*prerenal azotemia.* For the serum sodium to rise from 140 to 170 m Eq/L., more than 20 percent of the body water must be lost. Under these circumstances the blood pressure is often depressed and glomerular filtration rate contracted. The blood urea nitrogen may rise to three or four times normal. The reduction in glomerular filtration rate consequent to dehydration may enable the urine to be concentrated up to or slightly beyond the osmolarity of plasma so that an underlying state of diabetes insipidus may be unappreciated.

A low grade *fever* occasionally accompanies hypernatremia, disappearing when proper hydration returns the serum sodium to normal.

The *cardiovascular effects* of hypernatremia are related largely to the decrease in blood volume secondary to dehydration. The electrocardiogram usually is unchanged, though infusions of hypertonic sodium chloride tend to correct certain electrocardiographic abnormalities seen in hyperkalemia[12] and quinidine intoxication.[13] Hypernatremia does not appear to affect cardiac performance in the intact dog.[14]

*Hypocalcemia* was reported by Finberg and Harrison in hypernatremic infants accidentally poisoned with sodium chloride.[7] It is not clear what the mechanism of the fall in serum calcium was in these children and hypocalcemia has not been a constant feature in other patients with an elevated serum sodium.

## HYPONATREMIA AND SODIUM DEPLETION

The subjective manifestations of sodium chloride deficiency in man have never been described more vividly than by R. A. McCance in 1936 when he produced sodium deficiency in himself and other normal volunteers by a salt free diet combined with sweating.[15] The low sodium regimen lasted for 11 days. During this time serum sodium fell from 147 to 131 m Eq/L. and serum chloride from 100 to 83 m Eq/L. Blood urea nitrogen rose from 15 to 42 milligrams percent. The net negative balance of sodium was about 800 milliequivalents and weight loss averaged 2 to 3 kilograms. Their experience is quoted below.

> The sense of flavor and taste was affected. E. interpreted this aberration or lack of sensation as thirst. She complained of it constantly and drank freely but without obtaining any relief . . . R. A. M. recognized the feeling as distinct from thirst. His mouth was not unduly dry but food was tasteless, even highly flavored food, and this was the more noticeable because such foods were eagerly sought to make the meals more appetizing. The distaste however was not confined to meals and was a feature of every waking hour. "Even cigarettes don't taste." . . . On the whole all slept well but R. A. M. and R. B. N. were apt to be roused by attacks of nocturnal diuresis and both were troubled by nightmares. R. A. M. was "never hungry." . . . Nausea accompanied almost every meal . . . R. A. M. suffered considerable abdominal discomfort. . . .
>
> Both the male subjects suffered considerably from cramps . . . not of the very localized type which are said to affect stokers and miners but were widespread, frequent, not very painful, and generally controllable. Any muscle in the body was liable to go into spasmotic contraction, especially if some little effort was demanded of it. . . . Perhaps the most characteristic of all were the manual cramps.

R. A. M. experienced "constant mild cramps of the fingers and thumb when using forceps at the balance." . . .

A mild breathlessness at first and sense of fatigue gave place later to general exhaustion and distress on the least exertion. R. A. M. found that going up two flights of stairs to the laboratory was a serious undertaking causing a sense of breathlessness and the most unpleasant feeling of constriction across the sternum which compelled him to stop and rest. Throughout the experiment he used to go for a measured walk for about a mile after breakfast .Toward the end of the deficient period the breathlessness and sense of constriction forced him to sit down and rest two or three times at a hill for which he would ordinarily not have slackened pace. Little acts of the daily routine produced a localized sense of fatigue; his "arm got tired shaving" and finally his "jaw got tired eating."

Mentally R. A. M. felt normal but R. B. N. felt "slow in the head" and showed it in his behavior. For several days he experienced at frequent intervals sensations of "deja vu." He became apathetic and his mental processes appeared to be dulled. . . .

In both subjects the resting pulse rate remained normal but the volume became very small. Both subjects had normal blood pressure and maintained them within narrow limits throughout the experiment. . . .

Recovery was quite dramatic. R. A. M. found his sense of flavor returned before he had finished his first salt meal. In a few hours he was much more comfortable and mounting the stairs and by evening was "no longer aware of his legs as he moved about the room." R. B. N. ate his first meal containing salt in the evening . . . after 48 hours he "jumped off the bus while it was going and ran up the stairs"—simple pleasures but keenly enough appreciated to make him record that he had "had a grand day."

*Cardiovascular and renal effects of hyponatremia.* The hemodynamic changes and the deterioration of renal function caused by sodium depletion are explained largely by the effects of a concomitant depletion of plasma volume on the cardiovascular system. It is doubtful whether sodium depletion can itself produce marked circulatory effects if it is not accompanied by a reduced plasma volume. In the syndrome of inappropriate secretion of antidiuretic hormone, in which plasma volume is usually normal or increased despite hyponatremia, there is no hypotension and no reduction in glomerular filtration rate. On the other hand there is evidence that in the presence of a contracted plasma volume the sodium concentration per se may influence the severity of the circulatory changes.[16,17] Such an influence might be exerted through effects of the sodium ion on the tone of vascular smooth muscle and its responsiveness to pressor substances.[18]

In the range of serum sodium commonly encountered, down to 100 mEq/ L., hyponatremia does not appear to affect the electrocardiogram in any consistent way. In hyponatremia due to sodium depletion, there is usually a reduced cardiac output and a tendency toward arterial hypotension.[19] Coronary flow, left ventricular work and cardiac efficiency are all reduced. There is a tendency to fainting because of postural hypotension. Vasoconstriction in the renal vascular bed leads to reduction in the renal plasma flow and glomerular filtration rate.[20] In experimental animals, sodium restriction leads to a preferential restriction of blood flow through cortical nephrons.[21] Urea clearance tends to be reduced proportionately more than filtration rate, perhaps because of the low urine flow, and the increased fractional reabsorp-

tion of glomerular filtrate in the proximal tubule; hence the blood urea nitrogen tends to rise rather rapidly. It is unusual to see elevations of BUN above 100 milligrams percent, however, unless the depletion has been severe enough to produce vascular collapse and anuria with tubular necrosis.[*]

In the typical patient with moderately severe salt depletion, urine volume is scanty and the osmolar concentration of urine is equal to or greater than that of plasma. There is sometimes slight proteinuria and the urinary sediment may contain hyaline and granular casts. The normal diurnal variation in urine volume is reversed so that nocturia may be present even though the total daily urine volume is low. Because of the circulatory impairment induced by depletion of extracellular and plasma volume, water diuresis is impaired despite the hypotonicity of body fluids. Water without salt given to a salt-depleted patient may, therefore, merely accentuate the hyponatremia, as in the following illustrative case:

A 48 year old man underwent bilateral lumbodorsal sympathectomy for malignant hypertensive cardiovascular disease. Before the operation his blood urea nitrogen was 20 milligrams per 100 milliliters and repeated urinalysis revealed only a trace of albumin. Serum sodium was normal. After the operation he vomited on several occasions and was unable to take nourishment by mouth. There was profuse sweating from the upper half of the body associated with a low grade fever. Several liters of glucose and water were administered each day. Urine output was always greater than one liter per day. It was noted that the blood urea nitrogen was rising steadily. On the 8th postoperative day he was confused and somnolent. There were no signs of dehydration. The blood pressure was 140/80, the blood urea nitrogen 63 milligrams per 100 milliliters, the serum sodium 119 mEq/L., chloride 80 mEq/L., bicarbonate 32 mEq/L., and potassium 3.7 mEq/L.

In the course of the next two days 50 grams (862 milliequivalents) of sodium chloride were given intravenously in a total volume of two liters. The patient's condition rapidly improved thereafter despite the transient appearance of dyspnea, tachycardia and pulmonary rales. Blood pressure rose, urinary output increased, and the mental confusion cleared. The blood urea began a steady decline. Six days later the blood urea nitrogen was 25 milligrams per 100 milliliters, serum sodium was 42 mEq/L., chloride 101 mEq/L., and bicarbonate 32 mEq/L. Signs and symptoms of congestive heart failure had disappeared and the blood pressure was stabilized at moderately high levels.

*Gastrointestinal symptoms.* Loss of appetite, nausea, and vomiting frequently accompany hyponatremia. A low serum sodium should therefore be suspected when, for example, anorexia follows administration of a diuretic or nausea appears in a patient with impaired renal function who is asked to take a low salt diet. Abdominal cramps may occur. The combination of nausea, vomiting, and abdominal pains, often limit the further ingestion of water, as was the case when Jaenicke and Waterhouse tried to produce hyponatremia by excessive water intake combined with injections of long acting vasopressin in human subjects.[*] Gastric emptying time is said to remain normal despite moderately severe sodium depletion.[*] Diarrhea is not a usual symptom of hyponatremia or sodium depletion although occasionally it is seen in acute instances of severe water intoxication. When diarrhea is present, therefore, it is likely to be a cause rather than a result of hyponatremia. The peculiar thirst described in many instances of salt depletion probably is due to contraction of body fluids since it is not seen in most cases of inappropriate secretion of antidiuretic hormone, where serum sodium is low but body water increased. Intense salivation is a rare accompaniment of massive water intoxication.

*Neuromuscular and central nervous system signs of hyponatremia.* The neurological symptoms of hyponatremia are correlated with the level of serum sodium and the rapidity of its fall rather than with the presence or absence of contraction of the plasma volume. They therefore appear with equal frequency in hyponatremia resulting from sodium depletion and in hyponatremia due primarily to dilution of body fluids with water. A rapid fall of serum sodium to a level of, say, 128 to 130 mEq/L. may be associated with distinct and disturbing neurological signs, as in the experiments of McCance quoted above. On the other hand, when hyponatremia has developed slowly, the serum sodium may fall as low as 110 mEq/L. before neurological symptoms are obvious.

Dizziness and headaches may be prominent. The CSF pressure is often elevated, presumably because of swelling of the brain owing to overhydration of cells, and papilledema may be seen.[25] Nevertheless, the cerebrospinal fluid protein is usually normal.

Weakness, lethargy, restlessness, confusion, and delirium, usually mark the progressive deterioration of cerebral function as hyponatremia develops and worsens. The ability to perform simple tasks like mental arithmetic is impaired. The patient may be unable to recognize his doctor or his relatives even though able to carry on a conversation.

Muscular twitches and tremors may be particularly troublesome in certain cases of hyponatremia.[26] These need not be accompanied by the muscle cramps that are so prominent in some cases of water intoxication. They sometimes mimic the jactitations of uremia. Hyponatremia predisposes to convulsions. The seizures are occasionally heralded by muscular twitches but more often appear explosively *de novo* as the first warning of a low serum sodium. They may be generalized or focal. The electroencephalogram usually shows diffuse abnormalities, including an irregular slow pattern,[27] low frequency activity and increased excitability,[28] but it can also sometimes be normal.[29]

Because hyponatremia may complicate diseases of the central nervous system, it is important to remember that symptoms and signs referable to the low serum sodium include a wide variety of focal as well as diffuse manifestations. For example, aphasia,[30] hyporeflexia,[30] hyperreflexia,[30] generalized rigidity,[31] ataxia,[33] and staggering[33] may all occur. Focal signs suggesting a localized lesion, including hemiparesis,[34] focal weakness and unilateral Babinski's sign,[31] have all been reported. The importance of correcting hyponatremia before making a final judgement about the nature and extent of neurological deficits is obvious.

### HYPOKALEMIA AND POTASSIUM DEPLETION

Neuromuscular symptoms are prominent in severe hypokalemia but are not usually seen before the serum potassium has descended to the neighborhood of 2.5 mEq/L. Below this level, some degree of muscular weakness is common. The weakness follows a distinctive pattern. Muscles innervated by cranial nerves are almost never affected.[35] The weakness is most prominent in the legs, especially the quadriceps muscles. For example, in a case of chronic potassium depletion due to laxative addiction where the serum

potassium was 1.7 mEq/L., the grip was said to be remarkably good and flexion of the elbows and dorsiflexion of the wrists surprisingly strong. The legs, however, were so weak that the patient was unable to lift them or to flex her hips.[36] With profound potassium depletion the respiratory muscles become involved. The diaphragm becomes paralyzed before the intercostal and accessory muscles of respiration.[37] As respiratory function is progressively impaired, "fishmouth" breathing, characterized by pursing of the lips, occurs.[38] Death may be caused by respiratory failure.

Despite the prominence of muscle weakness, deep tendon reflexes are usually present. The abdominal and cremasteric reflexes are not impaired.[35] Muscle cramps and paresthesias may be extraordinarily troublesome even when weakness is not marked. Muscular pains may so dominate the clinical picture as to prompt a mistaken diagnosis of "arthritis" or "rheumatism." The muscles are often tender. In familial periodic paralysis, but not in other forms of hypokalemia, the muscles sometimes appear to swell and have a firm rubbery consistency.[39] Chronic, long-standing potassium depletion can result in muscle atrophy.[40,41] Presumably this reflects pathological changes of the same kind that are seen in the skeletal muscles of experimental animals.[42]

The signs of latent tetany (Chvostek's and Trousseau's signs) can be elicited in certain patients with severe potassium depletion. The tetany is not due to concomitant deficiencies of magnesium and calcium since serum levels of these ions may be normal.[43] Interestingly, signs of tetany often become more prominent during the first 24 to 48 hours after potassium repletion has begun.[44] When serum calcium is low, potassium replacement may "uncover" tetany, a reflection of the antagonistic effects on neuromuscular excitability of potassium and calcium.[45]

Potassium depletion exerts its effects on muscle and nerve through at least two mechanisms. The *first* is through changes in the resting membrane potential. Since this is proportional to the logarithm of the ratio of the external potassium concentration to the internal potassium concentration, small changes in the concentration of potassium in extracellular fluid will obviously be more important than small changes in the already high concentration of potassium inside of cells (see Fig. 1). *Secondly,* changes in the intracellular concentration of potassium probably influence cellular function by altering the operation of intracellular enzymes. Small decreases in intracellular potassium greatly affect the rate of synthesis of macromolecules, including protein, RNA and DNA.[46]

Changes in cerebral function in potassium-deficient patients include lethargy, apathy, drowsiness, confusion, and irritability.[47] Coma, delirium, and hallucinations are more rare. It is interesting that cerebral symptoms are not usually part of the picture of familial periodic paralysis despite profound hypokalemia in this disease. Since potassium balance is usually normal in periodic paralysis but markedly negative in other forms of hypokalemia it is possible that depletion of the central nervous system is partly responsible for cerebral symptoms when the serum potassium is low. Whether the brain participates in the potassium deficit accompanying whole body potassium depletion is uncertain.[48,48a] It is conceivable that stupor or coma responding dramatically in certain patients to potassium replacement

| RESTING CONDITIONS | NORMAL | K DEFICIENCY | | K INTOXICATION | |
|---|---|---|---|---|---|
| | | ACUTE | CHRONIC | ACUTE | CHRONIC |
| $\dfrac{[K]i}{[K]e}$ | $\dfrac{160}{4.5}$ 35 | $\dfrac{140}{2.0}$ 70 | $\dfrac{90}{2.0}$ 45 | $\dfrac{160}{12.5}$ 13 | $\dfrac{170}{8}$ 21 |
| K equil. pot. $E_k$ $= -61.5 \log \dfrac{[K]i}{[K]e}$ | -95 mV | -113 mV | -102 mV | -68 mV | -82 mV |
| Membrane pot., $E_m$ $= -61.5 \log \dfrac{[K]i+0.01[Na]i}{[K]e+0.01[Na]e}$ | -88 mV | -100 mV | -88 mV | -65 mV | -77 mV |
| Excitability $= E_m - E_t$ | 88 - 65 23 mV | 100 - 65 35 mV | 88 - 65 23 mV | 65 - 65 0 | 77 - 65 12 |
| Electrochemical excitation | Normal | Hyper-polarization block: paralysis | Normal | Depolarization block: paralysis | Partial depolarization: hyperexcitability |

FIG. 1. *Neuromuscular excitability as a function of intracellular and extracellular concentrations of potassium.* The values given for [K]i and [K]e under various circumstances are illustrative only and do not represent actual data. From Seldin, Carter, and Rector, reference 78.

are due in part to effects of potassium upon the circulation (see below) or, in patients with cirrhosis of the liver, on the metabolism of ammonia.

The electroencephalogram is usually unaffected by hypokalemia but an abnormal EEG has rarely been observed associated with potassium depletion, with restoration to normal following the administration of potassium.[49]

*Renal function in potassium depletion.* The most important abnormality of renal function is the inability to concentrate the urine normally.[50] When potassium is restricted in the diet of normal young men, significant hyposthenuria is apparent as early as the fourth day in occasional subjects and is present in all by the second week.[51] Impairment of concentrating ability is usually slight until approximately 200 mEq. of potassium has been lost (Figures 2-3). By the time 400 to 600 mEq. have been lost, it is difficult for the kidneys to concentrate urine above the osmolality of plasma. Nocturia, polyuria, and polydipsia are consequently among the most common symptoms of potassium deficiency. The ability of the kidneys to dilute the urine, however, is well maintained. In certain patients, thirst appears to be present out of proportion to the impairment in concentrating ability and it has been proposed that in such patients the hypothalamic centers for thirst are affected;[52] perhaps, however, they are responding to the circula-
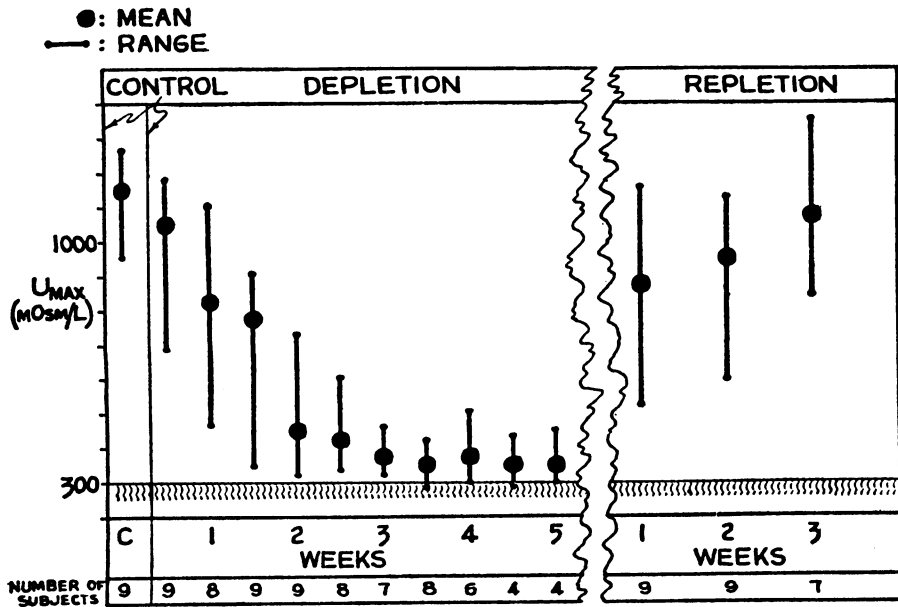
Fig. 2. *Reduction in concentrating ability* ($U_{max}$) *in normal subjects maintained on a diet deficient in potassium.* From Rubini, M., reference 51.
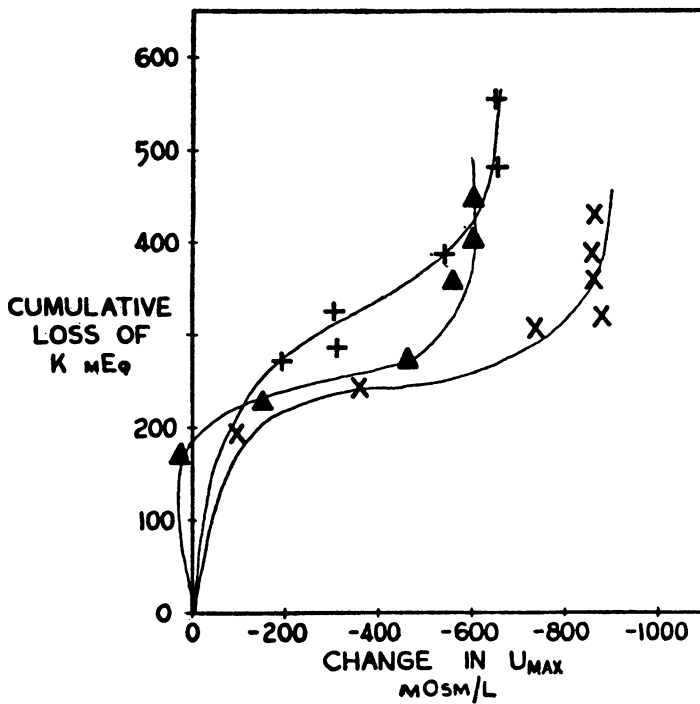


Fig. 3. *Relation of cumulative K deficit to concentrating ability in human subjects.*[51]

tory instability induced by a deficit of potassium. The mechanism of the reduction in concentrating ability appears to involve a diminution in the ability of the ascending loops of Henle to transport sodium into the interstitium of the renal medulla.[53]

Potassium deficiency also reduces the ability of the kidneys to excrete an acid load and to establish maximal concentration gradients of hydrogen ion between urine and plasma.[54] Thus it is unusual for a potassium-depleted patient to excrete urine with a pH as low as 5.0.

Prolonged potassium depletion produces some fall in glomerular filtration rate reflected in a drop in creatinine clearance and a rise in serum creatinine and blood urea nitrogen. Severe impairment of concentrating ability may exist, however, with a normal glomerular filtration rate. The decrease in filtration rate and renal blood flow are probably caused by swelling, vacuolation, necrosis, and subsequent scarring of cells lining the renal tubules.[55] In rats with potassium deficiency the collecting ducts seem most heavily involved[55] whereas in human patients with severe potassium depletion the proximal tubules are the site of intense water-clear vacuolation.[50]

Aminoaciduria has been found in a few patients with potassium depletion but has been shown to be absent in many others, hence the significance of this observation is uncertain.

The urinary sediment is usually benign. Slight proteinuria is occasionally present but this is not common. Potassium depletion does not impair the ability of the kidneys to conserve potassium. If extra-renal losses of potassium have caused the deficit, the concentration of potassium in the urine is usually below 10 mEq/L.

The muscular paralysis associated with abrupt falls in serum potassium, as seen in familial periodic paralysis, sometimes affects the bladder. Patients in the grip of an attack of periodic paralysis are often unable to void and require catheterization.

In man and animals, potassium deficiency is associated with an increase in the output of ammonium into the urine and in some species with an increase in the concentration of glutaminase in the kidney. One result of this in patients who are unable to clear ammonia rapidly from the circulation, e.g., with hepatic cirrhosis or portal shunting, is that potassium deficiency induces a rise in blood ammonia. This may lead to rapid clinical deterioration when potassium deficiency induced by diarrhea or by a diuretic is superimposed upon an already precarious clinical state of hepatic insufficiency.[56]

*Cardiovascular changes.* Electrocardiographic changes are noted in the majority of patients with a serum potassium below 3 mEq/L. Virtually all changes in the electrocardiogram are rapidly reversed when the potassium deficit has been corrected (Fig. 4). Electrocardiographic abnormalities include:[13,57-59]

1. depression of the ST segment;
2. lowering, flattening or inversion of the T wave;
3. presence of an elevated (greater than 1 mm.) U wave, which may be responsible for the impression of a prolonged QT interval;
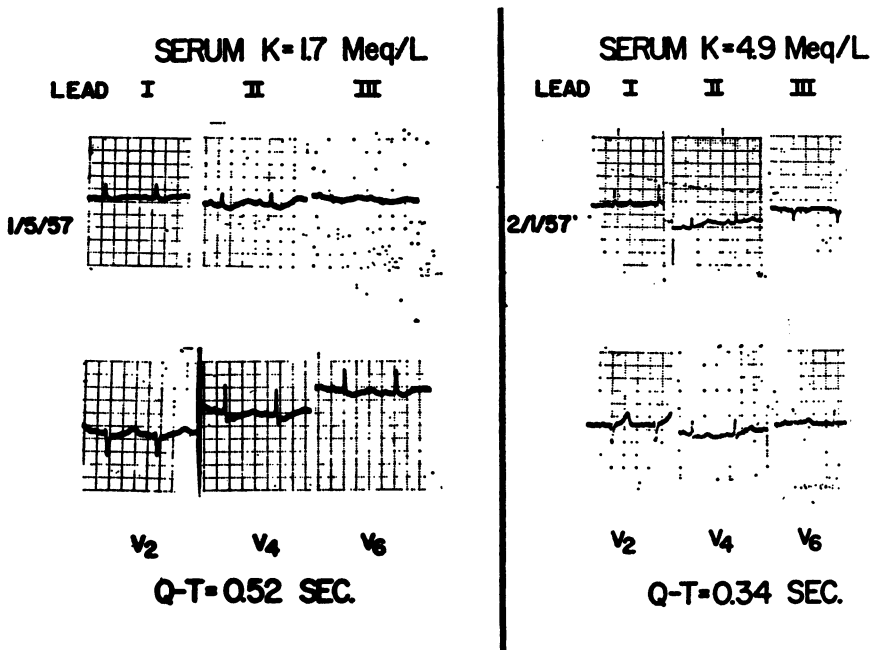
Fig. 4. *Electrocardiogram before and after correction of hypokalemia.* Note prolongation of the Q-T interval and flattening of the T-wave in all leads, which disappeared after treatment of potassium depletion.

4. the appearance of prolongation of the QT interval may occur because of T wave flattening with a large U wave . . . the QU interval thus seeming to be the QT interval, resembling hypocalcemia;
5. tall, narrow peaked U waves in the precordial leads (rare);
6. increase in P wave amplitude;
7. prolongation of PR interval; and
8. prolongation of the QRS period by 0.1 to 0.3 seconds, without changes in QRS configuration.

Severe hypokalemia may produce arrhythmias that can be detected at the bedside. A sinus brachycardia is sometimes seen, accentuated by increased sensitivity to vagal stimulation. Prolongation of the PR interval and dropped beats can sometimes be abolished by atropine; however, atropine does not affect the abnormal T waves.[60] Second degree AV block with the Wenckebach phenomenon has also been observed, presumably due also to increased vagal tone.[13] Atrial arrhythmias include auricular flutter and paroxysmal auricular tachycardia with block.[13,61] Atrioventricular dissociation and even ventricular fibrillation have been observed. These arrhythmias, commonly associated with digitalis toxicity, may be observed in the absence of digitalis when severe potassium deficiency with hypokalemia are present.

Although myocardial necrosis is a constant finding in severe potassium depletion in rats, the electrocardiographic changes just enumerated prob-

ably reflect changes in serum potassium rather than in the intracellular stores of potassium in the myocardium. EKG changes are prominent in familial periodic paralysis where the body stores of potassium are not depleted.[62] Congestive heart failure is not encountered in the vast majority of patients with potassium depletion, although scattered areas of necrosis in the myocardium have been described in patients dying with severe potassium deficiency. An increase in cardiac size, sometimes accompanied by a systolic murmur, has been noted in certain patients with hypokalemia due to periodic
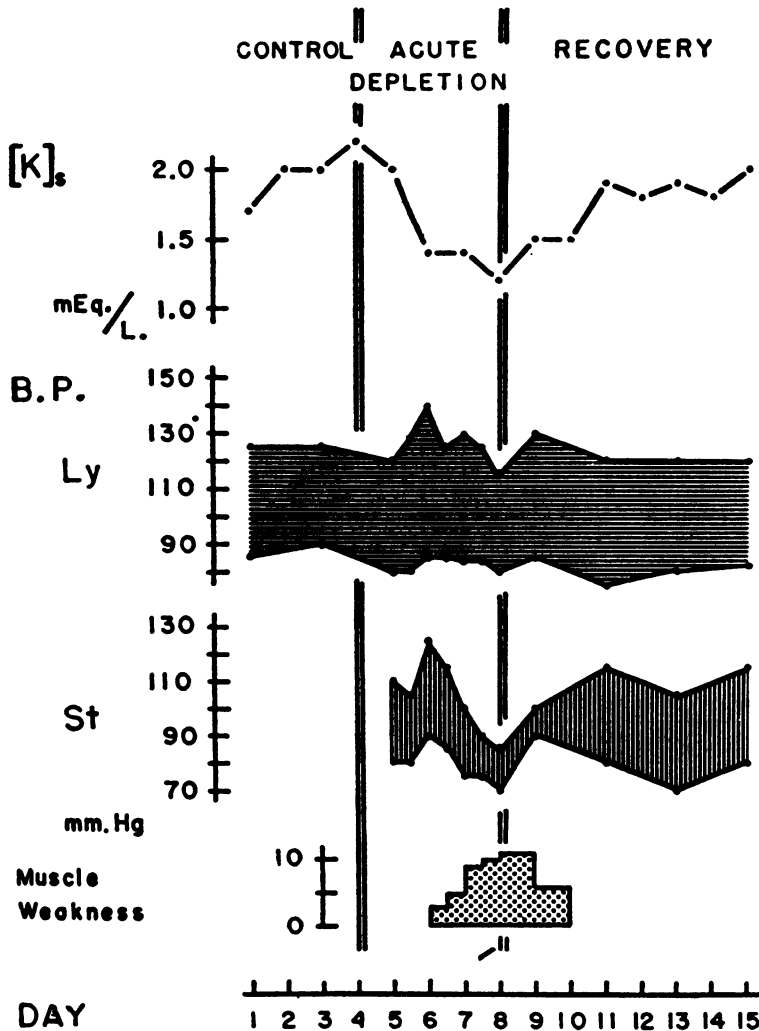


FIG. 5. *Severe postural hypotension and muscular weakness associated with acute depletion of potassium disappeared when partial repletion of potassium was accomplished.*[67]

paralysis or severe potassium deficiency, disappearing when potassium was given.[63,64]

Postural hypotension, by contrast, is common. The normal blood pressure overshoot in response to the Valsalva maneuver is abolished.[65] Dizziness and a tendency to fainting are common symptoms (Fig. 5). An important consequence of this effect of potassium deficiency on blood pressure is the susceptibility of patients to post-operative shock. The effect is not due to hypokalemia alone, since hypotension is not a feature of periodic paralysis. The vascular response to catecholamines and other pressor substances is reduced in potassium deficiency.

The tendency to edema formation noticeable in many patients with potassium depletion is probably an expression of the cardiovascular effects of potassium deficiency. Gross pitting edema is uncommon but mild degrees of ankle swelling are frequently seen and the tendency to accumulate fluid in the upright position and excrete it when supine probably contributes to the nocturia that troubles many patients.

*Carbohydrate metabolism.* Potassium depletion tends to impair carbohydrate tolerance, causing mildly elevated fasting blood sugars and glucose tolerance curves which are diabetic in type.[66] The mild diabetes sometimes induced by diuretics can in many instances be partly or completely reversed by providing potassium supplements.

*Gastrointestinal symptoms.* Evaluation of abdominal symptoms is difficult when the serum potassium is low. Loss of gastrointestinal fluids often causes hypokalemia, and since potassium depletion itself produces ileus and vomiting, a vicious circle may aggravate electrolyte deficits.

Anorexia and nausea, progressing to vomiting, are common. The motility of the bowel is decreased. Prolonged gastric emptying, failure to pass stools or gas, distention, abdominal cramps and paralytic ileus, may all be produced by potassium depletion alone. The clinical signs, including x-ray evidence of dilated bowel, are easy to confuse with those of intestinal obstruction or peritonitis. The abdominal distention is usually unresponsive to neostigmine,[67] while decompression by nasal gastric suction is often ineffective and may accelerate the process of depletion. Weakness of the smooth muscles of the gastrointestinal tract and impairment of the response to parasympathetic stimulation are the basis of the symptoms. Replacement of potassium prompts immediate return of bowel sounds with frequent voluminous bowel movements and subsidence of distention.[68]

## HYPERKALEMIA

The effect of hyperkalemia that overshadows all others in clinical importance is its influence on the electrical impulse propagating the heart beat. The danger of hyperkalemia is that patients will die of cardiac standstill or arrhythmia.

The effects of an elevated serum potassium on the heart are usually unimportant below 7 mEq/L. but are almost always present above 8 mEq/L. They are heralded by characteristic changes in the electrocardiogram, illustrated in Figure 6. The initial change is the appearance of high, peaked T waves, especially pronounced in the chest leads.[69] These may be differentiated from other disorders causing an increase in the amplitude of the T
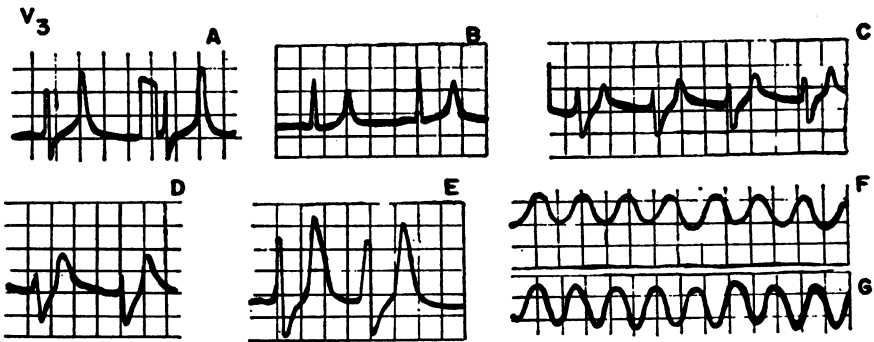
FIG. 6. *Representative electrocardiograms in potassium intoxication.* (From Merrill, J. P.: The Treatment of Renal Failure. New York, Grune and Stratton, 1965.) In general, the changes are sequential. The earliest change is the development of peaked T-waves (A and B). The S-wave may increase in depth and the S-T segment becomes depressed (C). The P wave disappears and the QRS complex lengthens (D and E). Ventricular flutter or tachycardia finally supervene (F and G).

wave by a normal or decreased Q-T interval, whereas in other conditions the Q-T interval is prolonged.[13] As serum potassium rises, the P-R interval becomes prolonged.[70] This is followed by disappearance of the P waves, and finally decomposition and prolongation of the QRS complex.[71] Complete heart block may accompany an elevated serum potassium and disappear when hyperkalemia is relieved. Occasionally an apparent elevation of the R-ST junction and a coved RS-T segment may simulate an acute injury pattern, suggesting myocardial infarction or pericarditis.[72] Ectopic beats of the premature and/or escape type may also appear.[73] At levels of serum potassium above 9 or 10 mEq/L., the QRS complex becomes smooth, wide and sinuous, joining with the T wave and resulting in a continuous sine wave appearance. This is thought to represent a form of ventricular flutter and progresses to ventricular fibrillation or standstill.[74]

In addition to the classical changes in the electrocardiogram, there is evidence that hyperkalemia renders the heart more susceptible to vagal standstill. This may be the explanation of some instances of sudden death in the course of hyperkalemia in the absence of premonitory electrocardiographic signs.

The electrocardiographic changes of hyperkalemia are exaggerated by a low serum sodium and a low serum calcium, as well as by acidosis and an elevated level of serum magnesium. They are counteracted by a high serum calcium. Calcium infusion is therefore a useful measure in the emergency treatment of severe hyperkalemia.

Although the electrocardiographic changes of hyperkalemia are frequently helpful, they may be misleading. One can demonstrate the regression of the electrocardiographic signs of hyperkalemia (peaked T waves) in a patient with renal failure, despite an increase in the level of serum potassium. The improvement shown in the electrocardiogram can occur in conjunction with treatment of acidosis and hyponatremia.
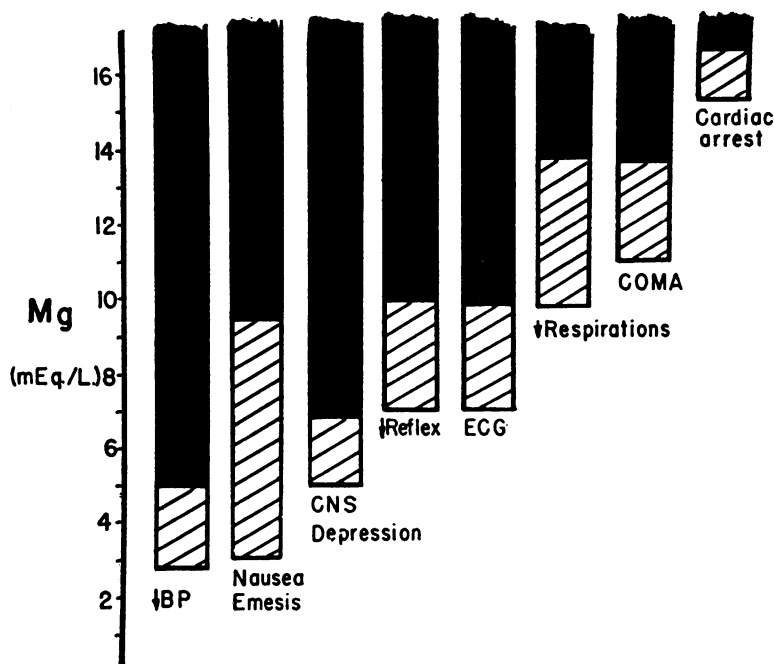
FIG. 7. *Signs and symptoms of magnesium intoxication.* From Randall, R. E., Jr., reference 151. The hatched areas represent the variable serum concentrations at which the toxic phenomena may occur during the infusion of magnesium and the solid areas imply uniform occurrence of the phenomena at the concentrations represented.

Although cardiac performance may be altered because of arrhythmias and conduction changes, hyperkalemia *per se* does not appear to interfere with cardiac contractility. Goodyer found that in intact dogs an increase in serum potassium to the range of 8.4 to 11.5 mEq/L. had no significant effect upon ventricular contractile strength, even in the presence of marked electro-cardiographic abnormalities.[14]

*Neuromuscular signs.* A Landry type of rapidly ascending muscular weakness that leads to flaccid quadriplegia (although cerebration and cranial nerve function are not affected) is observed occasionally with the very high serum potassium levels that sometimes accompany either renal insufficiency or Addison's disease.[75] In such patients, the serum potassium is over 7 and usually above 8.5 mEq/L. The cerebrospinal fluid is normal. Paresthesias are sometimes present.[76] Vibratory and position sense as well as cutaneous sensory perception may be diminished or absent. Usually, however, no objective sensory abnormalities are noted. The deep tendon reflexes may be elicited early, when weakness is present but before paralysis has occurred. Respiratory paralysis and involvement of the muscles of phonation have been described.

In the rare inherited condition of hyperkalemic periodic paralysis,[77] stiffness and weakness occur most often after exercise and during sleep. The

spontaneously occurring episodes of weakness can be provoked by oral potassium loads. The serum potassium in such patients is normal or only slightly elevated during an attack and the condition appears to be due to some special susceptibility to levels of serum potassium that are borne with equanimity by normal people.

The mechanism of the effects of both hyper- and hypokalemia on neuromuscular excitability can best be understood by reference to Figure 1.[78] The excitability of neuromuscular tissue is defined as the difference between the membrane potential $E_M$ and the threshold potential $E_T$. Alterations in potassium change membrane excitability only through changes in the resting membrane potential $E_M$ and do not alter the threshold potential $E_T$. During excitation the discharge of acetylcholine at neural junctions and motor end plates depolarizes the membrane and lowers $E_M$. When $E_M$ is reduced to about −65 millivolts (the threshold potential), the tissue is activated. Therefore, any factor which increases $E_M$ or decreases $E_T$ will render the tissue less excitable, while factors that lower $E_M$ or raise $E_T$ will enhance excitability. Severe acute hyperkalemia lowers $E_M$ close to the level of $E_T$ and thereby induces a depolarization block with paralysis and defects in ventricular conduction.

## HYPERCALCEMIA

*Neurological and psychiatric signs and symptoms.* The records of patients with hyperparathyroidism or vitamin D intoxication leave a forcible impression of the large number and variety of psychiatric disturbances. In general, the symptoms are proportional to the degree of elevation of the serum calcium. Certain patients, however, become profoundly disturbed when the serum calcium is only 12 milligrams percent while others behave perfectly normally with a serum calcium of 16 milligrams percent.

Tiredness, listlessness, lethargy, apathy and depression are frequently observed. Other patients are agitated, nervous, and complain of insomnia. As hypercalcemia becomes more severe, delirium, confusion and somnolence progress to coma. Neurotic behaviour, slow mentation, psychomotor retardation, agitated depression, hallucinations and paranoia have all been documented in hypercalcemia and shown to be reversible when the hypercalcemia was controlled.[79–82]

Headache occurs frequently; it was reported, for example, in one fifth of a large series of patients with hyperparathyroidism.[80] The headache may be particularly severe in hypercalcemic crisis where it is exacerbated by the vomiting and dehydration that regularly accompany this disorder. Hypercalcemia alone may elevate cerebrospinal fluid protein.[83] Thus, when hypercalcemia complicates cancer, the combination of disturbed consciousness, headache, and increased CSF protein may suggest a cerebral metastasis when in fact the symptoms are due to hypercalcemia and are reversible.

Convulsions sometimes occur in hypercalcemia but they are rare. Focal seizures have been ascribed to clotting of small blood vessels within the brain.[84] Acute hypercalcemia is attended by a generalized tendency to thrombosis, due in part to rapid dehydration.[85]

Generalized muscular weakness is common. The patient complains that his strength has diminished, that he tires more easily, and that his legs

seem heavy. The proximal muscles and legs tend to be involved more than the muscles of the arms and the face. The muscles are not tender and show no atrophy. Aches and pains in the muscles are so prominent in a few patients as to raise the suspicion of a generalized process like periarteritis nodosa. When the serum calcium is above 15 milligrams percent, hypotonia may be noted and occasional patients are reported to have hyperflexible limbs.[86] The deep tendon reflexes show no consistent changes.

*Gastrointestinal manifestations.* Loss of appetite, nausea and vomiting usually accompany hypercalcemia. Anorexia and loss of weight, for example, are early signals of overdosage with vitamin D in the treatment of hypoparathyroidism. Abdominal pain may be so severe that patients are admitted to the hospital as abdominal emergencies to undergo laparotomy.[87] Severe hypercalcemic crisis may be complicated by abdominal distention and ileus. With more moderate hypercalcemia constipation is commonly noted; it occurred in 7 of 35 patients with vitamin D poisoning reported by Anning and his co-workers,[88] and probably results from a reduction in tone of the smooth muscle of the bowel and from dehydration. Loose stools and diarrhea are unusual. Increased salivation and difficulty in swallowing are occasionally encountered.

There appears to be an association between hyperparathyroidism and pancreatitis although pancreatitis is associated only rarely with hypercalcemia from other causes.[89] Hemorrhagic pancreatitis is found postmortem in one third of patients dying from acute hyperparathyroid crisis.[90]

Hypercalcemia increases the secretion of acid and pepsin by the stomach.[91] It is therefore not surprising that symptoms similar to those of peptic ulcer occur in a sizable minority of all patients with chronic elevation of serum calcium. The incidence of peptic ulcers in hyperparathyroidism varies from 8 to 25 percent.[92] Conversely, 1.3 percent of 300 patients with peptic ulcer are shown to have a parathyroid adenoma.[93]

*Cardiovascular system.* Acute hypercalcemia induced, for example, by the infusion of calcium salts in the usual Howard test, results in a systolic blood pressure rise of at least 30 millimeters of mercury in about half of the patients.[94] A local action of calcium on peripheral blood vessels to increase vascular resistance is probably partly responsible;[95] more important may be the effect of calcium to promote the release of catecholamines.[96] Hypercalcemic crisis, therefore, sometimes is associated with hypertension that disappears when the serum calcium returns to normal.[97] Hypertension is present in one third to one half of all patients with chronic hypercalcemia regardless of etiology, but in most cases it is caused by renal scarring secondary to hypercalcemic nephropathy, and it persists when the hypercalcemia is cured.[98]

The most notable electrocardiographic change is shortening of the QT interval.[99] The distance from the Q wave to the origin of the T wave is said to be inversely proportional to the level of serum calcium up to levels as high as 20 milligrams percent.[13,100] The PR interval sometimes is prolonged. A variety of arrhythmias may complicate hypercalcemia, especially when the serum calcium rises abruptly.[101,102]

The positive inotropic effect of digitalis is enhanced by calcium, but more important, digitalis toxicity is aggravated by hypercalcemia.[103] It may be

necessary to give calcium intravenously to certain patients who are already digitalized, as in renal insufficiency, but great care should be taken to avoid a rise in the serum calcium above 10 milligrams percent.

*Ocular manifestations.*[104] A diagnosis of chronic hypercalcemia often can be made at the bedside from the characteristic corneal and conjunctival deposits of calcium. Small, glass-like, crystal-clear particles are seen within the ocular conjunctiva in the region of the palpebral fissure. In the cornea there are hazy, greyish or whitish granular opacities in the form of a crescent running concentrically with the limbus on the nasal or temporal side or both, densest at the periphery and fading out centrally.[105] These resemble band keratitis ordinarily seen in association with intraocular inflammation. They are superficially similar to arcus senilis except that the latter is most prominent at the superior and inferior borders of the cornea while band keratopathy is most marked at the latter and medial margins. The opacities can be seen with the naked eye and with a strongly positive lens correction on the ophthalmoscope, but are most easily delineated by slit lamp examination. They represent precipitates of calcium phosphate salts. Precipitation occurs at the surface of the eye because the $pCO_2$ here is low and the pH alkaline. The conjunctival deposits sometimes produce intense irritation with redness and watering of the eyes. The lesions have been detected within only two weeks after vitamin D had been given in toxic doses. They disappear slowly after hypercalcemia has been controlled.

*Itching* is an annoying problem in a few patients with chronic hypercalcemia. It may be related in some cases to calcium deposits in the epidermis but it disappears so rapidly when the serum calcium is controlled that it seems more likely to be related to the hypercalcemia itself.[106]

### Clinical features of calcium nephropathy

Perhaps the most dramatic clinical example of the deleterious effect of hypercalcemia on the kidneys is hyperparathyroid crisis, where serum calcium concentrations as high as 18 or 20 milligrams percent may be associated with initial polyuria, followed by dehydration, oliguria, and rapidly advancing azotemia.[79,88,107] In contrast, prolonged hypercalcemia and/or hypercalciuria, associated with vitamin D intoxication, extensive paralysis, sarcoidosis, excessive ingestion of calcium and alkali, hyperthyroidism, or hyperparathyroidism may result in diffuse nephrocalcinosis and present as renal insufficiency insidious in onset and only slowly progressive. In such cases, severe impairment in renal function need not be associated with stones or even with radiologic evidence of calcification in the kidneys.

Of 45 patients with hyperparathyroidism reported by Hellstrom,[96] 37 had renal impairment as evidenced by an elevated blood nonprotein nitrogen or diminished ability to concentrate the urine. Polyuria and polydipsia may be so striking in hypercalcemic patients that diabetes insipidus is suspected.[96,108] These symptoms are often out of proportion to the degree of azotemia. It has been suggested that in some instances hypercalcemia may cause polyuria by producing thirst,[53] but in most cases in which these symptoms are prominent, kidneys are unable to concentrate the urine much above the osmolarity of plasma, even when vasopressin is injected. Impairment of maximum urinary concentration is usually an early sign of calcium nephropathy. Cer-

tain hypercalcemic patients seem to retain the ability to concentrate urine normally; this is especially likely to be the case, in our experience, when the serum calcium is below 13 milligrams percent, although an elevated serum calcium is not a prerequisite for the concentrating defect.

In more severe cases, there is usually a depression in glomerular filtration rate and renal plasma flow, without a change in filtration fraction.[109] The urinary sediment may contain red blood cells, as well as leukocytes and white blood cell casts, even when urine cultures are repeatedly sterile. Calcium phosphate casts are sometimes seen. In many patients, however, the urine may be remarkably free of abnormal formed elements. Unless congestive heart failure is present, proteinuria is slight. Moderate anemia, normocytic and normochromic in type, often appears in association with renal impairment.

The ability of the kidneys to secrete an acid urine and to manufacture ammonium in response to acidifying salts was noted to be dinminished in some hypercalcemic patients by Wong and Davies.[110] With the appearance of azotemia, the ability to conserve sodium may be impaired. This is not a prominent accompaniment of mild calcium nephropathy, however.

Extensive deposition of calcium in the renal substance with subsequent scarring results in persistent hypertension. Even if hypercalcemia is cured, such patients eventually may die from the effects of progressive vascular disease, although renal insufficiency may remit temporarily when the serum calcium is returned to normal.

**HYPOCALCEMIA**

*Tetany.* The cardinal manifestation of hypocalcemia, tetany is the expresson of excessive irritability of the motor nervous system. Hypocalcemia raises the threshold potential ($E_T$), thus decreasing the difference between $E_T$ and the resting membrane potential ($E_M$).[111] In its mildest forms tetany can be detected only by determination of the electrical reactions of muscles or by the presence of certain abnormal reflexes. In more outspoken cases, active spasms, varying from typical contractions of the extremities to generalized convulsions, are observed.

The earliest symptoms of tetany are frequently not motor but sensory. Numbness of the fingers is often the first complaint. Tingling and burning are felt in the extremities and about the lips and tongue. Cramps in the muscles of the extremities may be felt before tetanic spasm is actually seen. This parallels the sequence seen in the development of the Trousseau phenomenon, in which the regular order of occurrence is: tactile paresthesias, fasciculation, sensation of the spasm, and finally the spasm itself.[112] In typical carpopedal spasm (accoucheur's sign) the fingers are flexed at the metacarpophalangeal joints and forcibly extended at the interphalangeal joints. The thumb is extended midway between opposition and adduction, tightly pressing against the other fingers. In severe cases, the lower extremities become involved, with the thigh adducted, the hip and the knee extended and the foot and toes plantar-flexed. With tetany of the facial musculature the corners of the mouth are drawn down, the nasolabial folds accentuated, the eyes widely opened, the forehead transversely wrinkled, and the mouth pursed.

When tetany is latent, the spasm can be elicited by placing a blood pressure cuff around the arm and occluding arterial flow. Spasm occurring within five minutes is considered a positive Trousseau test. Chvostek noted in 1876 that latent tetany of the facial musculature could be uncovered by tapping over the facial nerve in front of the ear. When Chvostek's sign is fully positive, this results in contraction of the muscles of the eyelid, upper lip, alae nasi, and corner of the mouth, but in less pronounced cases the corner of the mouth with or without the alae nasi are affected alone.

*Laryngeal stridor,* producing hoarseness, frequently accompanies hypocalcemia. After neck surgery it is easily mistaken for vocal cord paralysis. Spasm of the laryngeal muscles producing dyspnea and cyanosis is probably the most common cause of death from severe hypocalcemia.

Because neuromuscular excitability is influenced by many factors in addition to the level of ionized calcium in extracellular fluid, the level of serum calcium at which tetany occurs is extremely variable. Children are more susceptible than adults. Intraarterial injection of adrenalin produces a marked local increase in the intensity of tetany and small amounts of adrenalin may produce laryngeal stridor in hypocalcemic patients.[113] For this reason, catecholamines should be given with the greatest caution when hypocalcemia is present.

*Convulsions* frequently occur without the preliminary warning of tetany. The seizures are usually generalized but they may be focal; in an analysis of 43 patients with hypocalcemic fits, 5 had some focal element.[114] The predominant finding in the electroencephalogram is the presence of slow waves at a frequency of 2 to 5 per second, which may dominate the entire record or alternate with the basic normal rhythm.[115] Spikes occurring in bursts may also be seen. Hyperventilation and photic stimulation activate these abnormalities. Interestingly, acute infusions of calcium have little or no effect on the abnormal EEG of hypocalcemia.

*Impairment of mental function* is an underemphasized consequences of hypocalcemia. Severe intellectual and emotional changes may occur in the absence of other signs or symptoms.[116] Chronic hypocalcemia in childhood may produce mental retardation as seen in certain cases of idiopathic and pseudo-hypoparathyroidism.[119] Severe psychosis may be seen 3 or 4 months after neck surgery in post-operative hypoparathyroidism resembling schizophrenia or manic-depressive states.[117,118] Emotional lability, apprehension and depression disappear when hypocalcemia is corrected. Any or all of these symptoms may occur in the absence of overt or latent tetany.[117,118] Interestingly, patients with post-operative hypocalcemia appear to have an increased susceptibility to the production of "visual after-images" by complex visual stimuli.[119] This may play a role in the production of hallucinations.

*Cerebrospinal fluid pressure* may be elevated in chronic hypocalcemia and papilledema may be present.[120,121] The CSF protein is normal.[120]

*Intracerebral calcification* is most frequently associated with idiopathic hypoparathyroidism and pseudohypoparathyroidism, probably because both of these conditions produce unrecognized hypocalcemia of long duration in childhood.[122] It occurs but is rarer in hypoparathyroidism of the post-operative variety.[123] The mechanism of this interesting phenomenon is entirely unexplained. The calcification is localized to the basal ganglia and is usually

most prominent in the head of the caudate nucleus. The dentate nucleus of the cerebellum may also be calcified. The deposits of calcium are heaviest in perivascular areas. It may be pertinent that the basal ganglia seem particularly prominent to calcification after nonspecific injury to the brain produced by carbon monoxide, anoxia, kernicterus, encephalitis, tuberous sclerosis, or toxoplasmosis.

In the majority of instances, calcification of the basal ganglia produces few or no symptoms, but chorea, athetosis and Parkinsonism may in certain cases be severe and sometimes disabling.[124] Patients with hypoparathyroidism are unusually susceptible to dystonic reactions to phenothiazine drugs even when they are normocalcemic; this may reflect subclinical changes in the function of the basal ganglia.[124a]

*Ocular manifestations.* A distressing complication of chronic hypocalcemia due to hypoparathyroidism is lenticular cataract. Cataracts may grow rapidly, over a period of two to three months after parathyroidectomy, or appear very slowly, after several years. Calcium is deposited underneath the anterior and posterior capsule as discrete opacities that later extend from the periphery of the lens toward the center. As the cataracts develop, the lens become more completely involved and the condition becomes indistinguishable from senile cataracts.[125] A less common manifestation of early lenticular involvement is saggital flattening of the lens.[126]

Keratitis and conjunctivitis producing photophobia and blepharospasm occur frequently.[127] Conjunctival changes are seen particularly in the syndrome of moniliasis, Addison's disease, and hypocalcemia.[128]

*Integument.* Thinning and loss of hair from all parts of the body is especially characteristic of untreated patients with idiopathic hypoparathyroidism.[129] The skin becomes dry, keratotic, and scaly, with a dermatitis resembling eczema, and appears particularly susceptible to infection with monilia.[130] Growth of the nails is slowed and the nails are shortened;[127] they become thickened, white, brittle, and chipped.[128] Transverse or longitudinal grooves may appear,[129] and the nails sometimes become atrophic and overgrown by skin.

When hypocalcemia is present in childhood, secondary to pseudohypoparathyroidism or the idiopathic variety, the teeth usually show marked dystrophic changes.[130] The deciduous teeth erupt in a delayed and irregular fashion and the permanent teeth are retarded in growth and development. Blunting of the roots of the molar teeth is especially characteristic. In adults, dental changes are less common although the teeth may become loose and fall out.[131]

*Cardiovascular manifestations.* The major electrocardiographic feature is prolongation of the QT interval owing to a widened ST segment that is isoelectric. The QRS complex is usually normal.[132]

Cardiac contractility is impaired by hypocalcemia. Rapid falls in serum calcium to low levels may produce heart failure, with enlargement of the heart and hypotension.[133,134] Pulmonary edema is a special danger, if at the same time the patient is being infused rapidly with sodium salts. This may occur, for example, in acute pancreatitis or as a complication of treating hypercalcemia with intravenous sodium phosphate.

*Gastrointestinal manifestations.* Disorders of bowel function usually cause hypocalcemia, rather than the reverse. In an occasional patient who has diarrhea, steatorrhea, and hypocalcemia, intestinal absorption seems to be improved when the hypocalcemia is properly treated.[135,136]

## DISORDERS OF MAGNESIUM METABOLISM

*Magnesium depletion and hypomagnesemia.* Magnesium depletion is not commonly encountered after brief dietary restriction because of the exceedingly efficient mechanisms of renal and gastrointestinal conservation. Symptomatic magnesium deficiency is likely to be seen only when decreased intake or absorption of magnesium are present together with increased losses.

The most careful studies of magnesium deficiency in man are those reported by Shils, who observed several patients in whom magnesium deficiency developed after they were fed for several months with a diet low in magnesium.[138,139] Hypomagnesemia was associated with episodic confusion. The patients became surly and irritable. They developed loss of appetite and sometimes vomited. In one patient, paralytic ileus appeared. Tremors and muscle fasciculations were observed in association with a positive Trousseau and Chvostek sign. Urinary incontinence in one man seemed to be associated with magnesium depletion since it disappeared when magnesium was given. Dependent purpura was seen in some patients. In these studies the serum magnesium fell to as low as 0.5 mEq/L. There was a consistent fall in serum potassium as well. Serum calcium decreased to 5 to 6 milligrams percent although the diet was not deficient in calcium or vitamin D.

It is not entirely clear whether the symptoms commonly ascribed to hypomagnesemia reflect the level of the serum magnesium alone, the concentration of magnesium in cerebrospinal fluid, or the intracellular concentration of magnesium in the tissue of nerves, brain and muscles. Certain patients whose renal conservation of magnesium is impaired can experience a rapid fall in the concentration of magnesium in plasma from the normal level of 2 mEq/L. to as low as 0.3 mEq/L. without symptoms.[137] In other patients, serum magnesium levels of 1 or 1.2 mEq/L. are associated with dramatic neurological manifestations.

*Neuromuscular manifestations.*[140] Tremors and seizures are classical signs of magnesium deficiency. The deep tendon reflexes are increased and clonus may be present. Difficulty with fine movements, muscular fasciculations, and irregular handwriting may appear.[141] Insomnia is sometimes a prominent and annoying complaint.

Convulsive seizures, usually generalized, but sometimes focal, serve most often as the dramatic event that calls attention to the magnesium deficit. The electroencephalogram is usually abnormal but the seizure patterns and diffuse dysrhythmias are not specific.[142]

Signs of tetany, including Chvostek's and Trousseau's sign, may be present, but the latter is less commonly seen. Frank carpopedal spasm is rare. The tetany, like the convulsions, does not respond to intravenous infusion of calcium.

Other neurological changes less consistently associated with hypomagnesemia include vertigo, ataxia, rigidity and cog-wheeling, nystagmus, and

dysarthria.[148,144] Bizarre involuntary muscular movements with athetoid and choreiform movements of the extremities and twitching of the face was considered by Flink a characteristic clinical feature of magnesium depletion.[145]

Changes in personality attributable to loss of magnesium may run the gamut from mild depression and nervousness to delirium, hallucinations, and psychosis.[141]

Although the picture of magnesium deficiency superficially resembles that of patients with chronic alcoholism and delirium tremens in whom serum magnesium may sometimes be low, magnesium replacement does not appear to be effective in treating most cases of delirium tremens. It appears unlikely that magnesium deficiency is primarily responsible for this disorder.[146,147]

*Cardiovascular signs.* Tachycardia of nodal or sinus origin is common in magnesium deficiency.[148] Premature atrial or ventricular beats may occur. Flattening or inversion of the T-waves, reversible when magnesium is administered, is especially prominent in children with protein-calorie malnutrition who rapidly develop magnesium deficiencies when they are refed.[148] Cutaneous flushing is a prominent sign of magnesium deficiency in rats,[149] though not in man, but it may have its analogy in the tendency to hypotension sometimes remarked in human patients.[141]

*Gastrointestoinal signs.* In patients with malabsorption syndromes like sprue or enteritis, the absorptive function of the bowel appears to be affected by the state of magnesium stores. Malabsorption is intensified by hypomagnesemia and improved when magnesium is repleted.[150] When adequate body stores of magnesium are assured in such patients the improvement in weight gain and general health may be striking.

*Changes in other serum electrolytes.* Magnesium deficiency in man is associated with a tendency to hypocalcemia. Resistance to parathyroid hormone appears to be involved, since the usual hypercalcemic and hyperphosphaturic response to infusion of parathyroid hormone is impaired.[150a] The normal response is restored by giving magnesium.

The tendency to mild hypokalemia seen in human patients who are magnesium deficient remains unexplained.

An illustrative case follows:

A 44 year old man was admitted after a generalized convulsion. He had had regional enteritis for 15 years. Twelve years before admission an ileocolostomy had been performed. Persistent diarrhea and spiking fever had prompted his recent admission to another hospital, where diseased bowel was resected three weeks before his convulsion. During convalescence from this operation, diarrhea continued, but food intake was poor.

On admission he seemed confused, and grimaced continually, jerking his left arm in what seemed like focal seizures. Chvostek and Trousseau signs were positive, and the serum calcium was measured and found to be 7.5 milligrams percent. Calcium was infused raising the serum calcium to 13 milligrams percent the next day, and 10 milligrams percent on the following day. Despite this, the state of consciousness did not improve, the positive Chvostek sign persisted, and he had another convulsion two days after admission, even though the serum calcium was now normal.

Magnesium deficiency was now belatedly suspected, and the concentration of magnesium was measured in the serum. It was 0.8 mEq/L.—half the normal level. During the next twelve hours he was given 120 milliequivalents magnesium as a 1 percent solution by intravenous infusion in glucose. By the next day he was awake, lucid and responsive. The serum magnesium was maintained at a normal level by injections of 32 milliequivalents of $MgSO_4 \cdot 8H_2O$ per day. Neuromuscular irritability disappeared. The patient's appetite returned. Interestingly enough, the diarrhea improved. He soon

left the hospital to the care of his private physician who gave him weekly injections of magnesium at home. In 3 months he had gained 30 pounds, and felt better and stronger than at any time in the past 10 years.

*Hypermagnesemia.*[151] An elevated level of magnesium in the serum occurs almost exclusively in patients who have renal insufficiency, either when renal failure is far advanced or under circumstances where patients are being treated with magnesium-containing salts or antacid mixtures. An excess of magnesium ions blocks neuromuscular transmission mainly by decreasing the amount of acetylcholine liberated at the neuromuscular function.[152]

At levels of serum magnesium between 3 and 5 mEq/L. there is a tendency to hypotension because of peripheral vasodilatation, often accompanied by a sensation of heat and thirst.[152] Nausea and vomiting may occur but are by no means constant (Fig. 7). At levels of serum magnesium between 5 and 7 mEq/L. patients become drowsy. This progresses to coma at 12 to 15 mEq/L. Intravenous magnesium sulfate has been used to produce surgical anesthesia. An analeptic such as pentamethylenetetrazole can reverse the central effects but has no effect on the peripheral manifestations.

The deep tendon reflexes are regularly lost when serum magnsium rises to about 7 mEq/L. Weakness and finally paralysis of all muscles supervene with progressively increasing concentration of magnesium. A curare-like effect, the paralysis may be counteracted with physostigmine.[153,154] The respiratory center is depressed at levels of magnesium greater than 10 mEq/L. Deep tendon reflexes invariably disappear before respirations are depressed. Thus, the presence of knee jerks can be relied on to indicate that there is a not a life-threatening hypermagnesemia. Conversely, magnesium should not be administered intravenously or orally to patients with impaired renal function if the deep tendon reflexes are absent.

Hypermagnesemia produces a variety of disturbances in the electrocardiogram in animals.[155,156] In man the QT interval may be prolonged and A-V and I-V conduction depressed. Cardiac arrest may be expected when the magnesium level exceeds 15 to 20 mEq/L. Intravenous magnesium sulfate injected into normal humans produces sinus bradycardia, prolonged PR interval, and increased sensitivity to vagal stimuli induced by carotid massage.

The association of elevated serum magnesium levels with uremia raises the possibility that some symptoms of renal insufficiency are secondary to the accumulation of magnesium. Infusions of magnesium into uremic patients (a time-tested method of treating uremic convulsions) caused in some an accentuation of nausea and malaise with increased drowsiness, lethargy and ataxia.[151] Postural hypotension became troublesome and it was difficult for some patients to void. Dialysis with subsequent lowering of the magnesium level relieved these symptoms. The mildly elevated levels of serum magnesium in most patients with uremic symptoms, however, do not suggest that magnesium intoxication plays an important part in symptomatology of renal failure.

## ACIDOSIS AND ALKALOSIS

*Acidosis.* The classical sign of systemic acidosis is the state of "fearful dyspnea" described by Kussmaul. The characteristic deep, sighing respirations reflect intense stimulation of the respiratory center. At a pH of 7.20,

pulmonary ventilation increases about four times; at a pH of 7.10, about 8 times.[157] The hyperpnea appears to affect the depth earlier than the rate of respiration. With lesser degrees of metabolic acidosis, the increased depth of breathing may be overlooked except by an experienced observer and the patient experiences no dyspnea at rest but becomes breathless on exertion. The intensity of respiration is related to the pH of blood and cerebrospinal fluid rather than to their bicarbonate content. Patients with chronic compensated metabolic acidosis, as for example in chronic renal insufficiency, may have easy respiration even with a serum bicarbonate below 10 mEq/L., while Kussmaul breathing is prominent in other patients with a higher blood bicarbonate in whom acidosis has developed abruptly and compensation has not yet taken place. When acidosis is extremely severe the function of the central nervous system is disrupted to such a degree that the respiratory center itself is depressed. An arterial pH more acid than about 6.8 is not compatible with life.

With progressive acidosis, consciousness is depressed and lethargy, disorientation, and stupor appear. These can usually be reversed promptly by infusions of alkali. Seizures are uncommon.

There is considerable evidence that the depression of the central nervous system seen in acidosis is related more closely to the pH of the spinal fluid than to the pH of blood.[158] For example, neurological symptoms are much more frequent and more profound in respiratory acidosis than in metabolic acidosis. In the former, acidosis regularly involves the brain as well as the blood, since $CO_2$ diffuses readily across the blood-brain barrier. In metabolic acidosis, on the other hand, cerebrospinal fluid pH is better defended.

Severe uncompensated respiratory acidosis produces a characteristic syndrome referred to as $CO_2$ narcosis.[159-161] Early symptoms are fatigue and weakness, succeeded by irritability, lethargy, and confusion. Headache is common, sometimes associated with blurring of vision. Mental derangements vary from depression and anxiety through somnolence to combative delirium. Abnormalities in the electroencephalogram include an abundance of activity in the slower frequency range, prominent theta waves, and slow alpha activity with increased or decreased voltage.[162] Tremors, jerking of the extremities, and clonic movements may occur.[163] Asterixis is characteristic. The cerebrospinal fluid pressure is often increased, perhaps a reflection of the increase in cerebral blood flow induced by carbon dioxide.[164] Papilledema and engorged retinal vessels may be seen on funduscopic examination.[162]

Systemic acidosis causes peripheral vasodilatation.[165] The skin may be warm and flushed, the heart rate rapid, and the pulse pressure wide. The cardiac output may be elevated initially but with profound acidosis it falls as hypotension becomes pronounced. As pH is reduced toward 6.8 in experimental animals, cardiac output is reduced because of a decrease in cardiac contractility[166] and slowing of the heart rate.[167] Bradycardia is probably the result of enhanced vagal effect during acidosis; the lowering of blood pH produces an inhibition of cholinesterase activity and consequent decrease in hydrolysis of acetylcholine.[168] Both the peripheral vessels and the heart are less responsive to catecholamines.[169] Patients who are acidotic also have a decreased responsiveness to catecholamines and restoring the

pH to normal allows a reduction in the amount of vasopressor necessary to support the blood pressure.[170,171]

Acute reduction of pH, due usually to rapid elevation of the $pCO_2$, is often associated with cardiac arrhythmia.[172] Other electrocardiographic changes include S-T depression, and changes in the height of the R and T waves.

Mild degrees of metabolic acidosis associated, for example, with a decrease in the serum bicarbonate below 20 mEq/L., are often accompanied by loss of appetite, nausea, headache, and lethargy. Such symptoms, occurring in patients with renal insufficiency, can be combatted by the prescription of small amounts of sodium bicarbonate. Chronic metabolic acidosis promotes the mobilization of calcium from the skeleton and its excretion into the urine or the feces.

Metabolic acidosis as severe as that present in diabetic coma interferes with carbohydrate metabolism and the action of insulin.[173] When blood pH is below 7.0, therefore, early infusion of sodium bicarbonate may be important not only in reversing coma but in allowing insulin to take effect.

*Alkalosis.* The predominant effect of a fall in hydrogen ion concentration in the extracellular fluid is an increase in irritability of the central and peripheral nervous systems. Following the rule that changes in $pCO_2$ are more rapidly and directly reflected in the cerebrospinal fluid than changes in blood bicarbonate, respiratory alkalosis is likely to be accompanied by much more dramatic symptoms than alkalosis of the same degree produced by metabolic causes.

Tetany caused by alkalosis is indistinguishable from that occurring in hypocalcemia. It is preceded by numbness and tingling of the extremities and the face around the mouth, and sometimes by tinnitus, cramps in the arms and legs and a warm feeling in the abdomen. Spontaneous contractions of the facial and mouth muscles, with dysarthria, have been reported.[174] In addition, patients with chronic hyperventilation, many of whom are hysterical, often complain of headache, dry mouth, inability to take a deep breath, chest pressure and pain, anxiety and apprehension. Some of these symptoms obviously reflect their psychiatric difficulties; others may be intensified by the respiratory alkalosis.

Convulsive tendencies are aggravated by alkalosis; hence petit mal or grand mal epilepsy may be provoked by hyperventilation.[175] Paroxysmal or continuous slow waves of high voltage are seen in the EEG, though the changes correlate poorly with arterial pH.[176]

Metabolic alkalosis tends to depress respiration though this is usually not apparent at the bedside. The ventilatory response to inhalations of carbon dioxide is regularly decreased.[177]

Changes in the electrocardiogram produced by alkalosis resemble those of hypokalemia and may be produced in part by the shift of potassium from an extracellular to an intracellular position. The T wave is usually flattened. The S-T segment may be prolonged and the delayed T wave closely followed by a P wave, producing the "T-P" phenomenon.[178,179]

Severe metabolic alkalosis is produced in patients with compensated hypercapnia secondary to chronic lung disease when ventilatory function is

suddenly improved with rapid lowering of the $pCO_2$ and consequent elevation of blood pH. Mental confusion and delirium, with focal or generalized seizures, cardiac arrhythmias and hypotension may complicate the systemic alkalosis. The symptoms are reversible if the $pCO_2$ is allowed to rise.[180] Chronic alkalosis produced by repeated vomiting can also be associated with delirium, obtundation, and seizures, but in such cases depletion of sodium and potassium and some degree of renal insufficiency also contribute to the picture.

Both respiratory and metabolic alkalosis regularly cause a fall in the concentration of phosphorus in serum and urine. This is particularly pronounced in the case of respiratory alkalosis.[181] Intracellular alkalosis enhances the activity of phosphofructokinase, a key enzyme regulating glycolysis.[182] The resulting increase in three-carbon phosphorylated compounds within cells causes inorganic phosphate to move into cells and out of the extracellular fluid. The ensuing hypophosphatemia is not known to cause any symptoms but the chemical finding may stimulate an unnecessary search for hyperparathyroidism.

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