Cardiac Changes in the Malnourished Child

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Protein-energy malnutrition (PEM) may have serious effects on cardiovascular structure and function. The purpose of this chapter is to review cardiac involvement from the standpoint of clinical manifestations, pathologic findings, laboratory investigations, experimental animal studies, and the effects of therapeutic interventions. Consideration will also be given to certain modifying factors such as deficiencies of essential vitamins, minerals, and other nutrients, as well as the potential influences of underlying infections. This topic has been the subject of two relatively recent reviews (1,2).

CLINICAL MANIFESTATIONS

In the marasmic form of PEM, there is a generalized wasting of muscle, including cardiac muscle, accompanied by the loss of subcutaneous fat and organ system atrophy. Total energy expenditure falls, and several endocrine adjustments take place, which result in the mobilization of fatty acids from adipose tissue and amino acids from muscle, including cardiac muscle (3). Hepatic gluconeogenesis is enhanced, and plasma proteins are maintained at normal levels (4). No edema occurs as long as the cardiac output is sufficient to maintain renal perfusion. Under these conditions, oncotic pressure will be unaffected, and extracellular water will not accumulate.

The signs of cardiovascular involvement in the marasmic form, which are evident in the infant, include weak peripheral arterial pulses and hypothermia secondary to low cardiac output and decreased total body metabolism (5). Blood pressure is low, with a narrow pulse pressure, further evidence of a low perfusion state. The terminal event may be circulatory collapse.

The clinical signs accompanying kwashiorkor differ from those seen in marasmus. While there is wasting of muscle, subcutaneous fat is present, and edema formation dominates the clinical picture in the somewhat older child. This clinical picture is thought to arise as a consequence of lowered serum albumin and a further fall in cardiac output, perhaps secondary to other nutrient deficiencies and/or infec-
tion. The adaptive endocrine responses are not as apparent as in marasmus, perhaps because the diet is more adequate in energy than in protein. Mobilization of fatty acids from fat depots and amino acids from muscle occurs but not to the same extent as in marasmus. The presence of proteinase inhibitors has also been described (6). The result of the amino acid deficit is decreased synthesis of plasma proteins, especially albumin, with a corresponding fall in oncotic pressure. Extracellular water accumulates, tissue pressure rises, and cardiac output falls. As renal perfusion pressure decreases, a series of events is initiated that lead to sodium retention via the renin–angiotensin–aldosterone system, which will further dilute the plasma proteins. This situation does not differ from that encountered in severe chronic liver disease, childhood nephrosis, constrictive pericarditis, and classic congestive heart failure.

The amount of peripheral edema observed in these patients can range from dorsal pedal edema alone to severe generalized anasarca. The infant or child appears pale or dusky, and there may be hypothermia and hypotension (5). The peripheral arterial pulsations are weak, and the precordial impulse is barely perceptible. Heart sounds are muffled and on occasion there may be a pericardial effusion and irregularities of cardiac rhythm. The above findings reflect a low cardiac output state, usually complicated by anemia and a low serum albumin that favors edema formation. The prominent clinical features of marasmus and kwashiorkor are summarized in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical features relevant to the cardiovascular system in PEM</th>
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<tbody>
<tr>
<td><strong>Marasmus</strong></td>
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<tr>
<td>Marked emaciation, no edema</td>
</tr>
<tr>
<td>Decreased oxygen consumption</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Bradycardia (unless fever present)</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Diminished arterial pulsations</td>
</tr>
<tr>
<td>Quiet precordium</td>
</tr>
<tr>
<td>Distant heart sounds</td>
</tr>
<tr>
<td>Systolic murmurs (anemia)</td>
</tr>
<tr>
<td><strong>Kwashiorkor</strong></td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Protuberant abdomen, ascites</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
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</table>
The findings on examination of heart muscle at autopsy are compatible with a generalized wasting process, with loss of cardiac mass proportional to the decrease in body weight (7-9). The heart is thin-walled, pale, and flabby and appears small in the untreated child. Epicardial fat is absent, while pericardial effusions are common in those patients with generalized edema. Cardiac dilatation may be observed, however, if death occurred during the course of acute therapy. The small heart size, prior to therapy, reflects the hypometabolic state, with reduced thyroid and adrenal activities (10,11). If demands are increased, as may occur with severe anemia, fever accompanying infection, or volume loading, then heart size may increase.

Histologic examination of heart muscle reveals thinning and shrinkage of myofibers in the marasmic patient, with interstitial edema in patients with kwashiorkor. Fatty infiltration of the liver is common.

A detailed study of the hearts of children who died from kwashiorkor revealed small fibers with poorly staining areas of the myocardium and indistinct striations, with vacuolization in many and deformed nuclei in others (7). When compared with children dying from other causes, the patients with PEM showed more vacuolization and had more interstitial edema. Other reports confirm the findings of a pale myocardium on gross examination and microscopic evidence of small fibers separated by edematous stroma (8). It would seem, therefore, that the heart in proven cases of PEM is almost always abnormal and probably represents the combined effects of malnutrition, anemia, and infectious disease processes.

Attention has been called to deaths that occurred suddenly following therapeutic intervention and apparent recovery (1,5). This raises the possibility of abnormalities in conduction tissue producing fatal disturbances of cardiac rhythm. Dysrhythmias could also result from acute perturbations in serum electrolytes, particularly sodium, potassium, calcium, and magnesium. The conduction system of the heart has been examined in cases of PEM by Sims (12). Atrophic changes were found, together with myocytolysis in the absence of accompanying cellular reaction or fibrous repair. Such abnormalities of the atrioventricular conduction system could certainly account for some of the unexplained sudden deaths.

Pathologic studies of PEM in the experimental animal model have revealed similar findings to those observed in the human experience. A PEM syndrome in young monkeys showed swelling and hydropic changes in the myofibers early in the pathologic process, together with eosinophilic coagulation and fragmentation of the sarcoplasm, hazy striations, small foci of necrosis, and infiltration with lymphocytes (13). As the deficiency syndrome progressed, atrophy of muscle fibers dominated the pathologic findings, with reduced heart size resulting from diminished muscle fiber size, without any diminution in the number of fibers present. The sarcoplasmic reticulum and sarcolemmal membrane were normal in these studies.

The various pathologic findings in PEM are shown in Table 2.
TABLE 2. The heart in PEM: cardiac pathology

Gross
- Small, pale, flabby myocardium
- Absent epicardial fat
- Pericardial effusion (if edematous)
- Normal coronary arteries, valves, and endocardium

Light microscopy
- Atrophy of myofibers, tightly packed
- Increase in connective tissue
- Fragmentation of myofibrils
- Loss of striations
- Patchy necrosis
- Interstitial edema (kwashiorkor)

Electron microscopy
- Foci of atrophy
- Loss of myofibrils and glycogen
- Decreased mitochondria
- Swelling of matrix and disruption of cristae

LABORATORY INVESTIGATIONS

On X-ray examination of the heart, the cardiac silhouette is usually small, as would be expected in a hypovolemic state and a generalized wasting process. There may be accompanying roentgenographic evidence of bronchopneumonia (6). Following therapy, cardiac size increases, and signs of pulmonary venous congestion may become evident.

The electrocardiogram usually shows sinus bradycardia and low voltages. Sinoatrioventricular conduction time may be short. The T waves often show decreased amplitude, with inversions over the left precordial leads (5). On occasion, ventricular ectopy, nodal rhythm, escape beats, and atrial fibrillation have been described. In one series, approximately half the patients had prolongation of the Q-T interval, possibly related to electrolyte abnormalities. Differentiating the effects of serious electrolyte imbalances and the protein energy deficit on the electrocardiogram is exceedingly difficult, since multiple deficiencies are usually present.

The echocardiographic features of PEM of diverse origins were described by Heymsfield et al. (14). These authors found that the absolute values for stroke volume and cardiac output were depressed, but when adjusted for body weight, the resultant indices were equivalent to those of matched controls. Indices of systolic function (ejection fraction, fiber shortening rate) were normal or enhanced. During therapy, these values remained normal, even when a state resembling congestive heart failure occurred, characterized by hypermetabolism, ventricular gallop rhythm, and an increased cardiac output.

Ventricular function and cardiac dimensions have also been studied in infants
with severe PEM by Shoukry et al. (15) using echocardiographically derived measurements prior to and following therapy. The results of these studies showed that infants with PEM, when compared with healthy controls matched for age and body length, had evidence of cardiac muscle atrophy and impairment of left ventricular systolic function. The latter was suggested by a slight reduction in fractional shortening, a systolic phase index of left ventricular function. During recovery, patients with PEM showed evidence of some increase in left ventricular mass and a slight increase in left ventricular end-diastolic dimension. The increase in septal wall thickness was most striking and approached the values observed in the control group. Shortening fraction also improved during recovery.

The salient radiologic, electrocardiographic, and echocardiographic findings in PEM are summarized in Table 3.

HEMODYNAMIC STUDIES

As previously cited, there is usually a hypometabolic state accompanying PEM, which is reflected primarily in bradycardia (heart rate under 50 beats per min) and hypothermia. This is part of an overall metabolic adaptation to conserve energy stores and body protein. Thyroid activity and adrenergic stimulation are depressed, the latter being a possible cause of a reduction in the inotropic state of the myocardium (10,11).

In terms of oxygen delivery to the tissues, the hypometabolic state would imply that the point or zone of critical oxygen transport (the product of cardiac output and
TABLE 4. The heart in PEM: myocardial performance

| Decrease in plasma and red blood cell volume |
| Decrease in chamber volume                   |
| Bradycardia                                  |
| Low cardiac output                           |
| Decreased pulmonary and systemic pressures   |
| Normal contractility                         |

arterial oxygen content) has been passed. There is now a parallel decline in total body oxygen consumption and oxygen transport. At this stage, the superimposition of increased oxygen demands (fever with infection) or anemia (decrease in oxygen content) would seriously compromise cardiovascular adaptation.

Plasma volume in the malnourished child is usually reduced, a complication of diarrhea, infection, and fluid and electrolyte shifts (16).

Hemodynamic studies in children carried out by Viart (17) showed bradycardia, hypotension in the pulmonary and systemic circulations, and a decrease in cardiac output. These observations reflect an adaptive low cardiac output state in line with a decrease in total body metabolism and a generalized wasting process. The metabolic and circulatory adjustments may be mediated by a decrease in sympathetic nerve activity and a state of relative hypothyroidism, as shown by decreased levels of thyroid hormone and catecholamines (10,11).

These laboratory data relative to the effects of PEM on myocardial performance seem to indicate that myocardial mechanics are normal and contractility intact in the face of the low cardiac output state. Pump function adjusted for body weight appears to be normal. If, however, interstitial edema or myofibrillar damage occurs secondary to very severe protein deprivation, or if there are complicating factors such as thiamine deficiency (unlikely) or anemia (likely), then myocardial compliance could well decrease, contractility become impaired, and congestive heart failure ensue.

The dominant hemodynamic observations in PEM are summarized in Table 4.

EXPERIMENTAL MODELS OF PEM

Experimental animal models of PEM have been developed, which have added to our understanding of the pathophysiologic processes involved in the syndrome. Morphologic, electrophysiologic, and biochemical changes in cardiac muscle have been studied by Rossi et al. (18–21) in the rat model of PEM. Rats fed on a low-protein diet for 6 weeks and compared with controls fed a high protein diet showed a severe restriction of body weight gain, with fatty liver and hypoproteinemia. In addition, striking myocardial pathologic changes, electrocardiographic abnormali-
ties, and increased myocardial catecholamine levels were observed, while the number of α- and β-receptors was unchanged. These authors postulate that prolonged nutritional stress raised myocardial catecholamine levels, which then played a role in the development of a myopathic process. This could explain some of the cardiac findings observed in protein-deficient rats. The morphologic observations included atrophy of myofibers with hyalinization and vacuolization on light microscopy. Small foci of necrosis, interstitial fibrosis, and mononuclear cell infiltration were occasionally seen. Ultrastructural lesions were characterized by myofibrillar degeneration, contraction band formation, dilatation of sarcoplasmic reticulum, mitochondrial swelling, dehiscence of intercalated discs, and widened interstitial spaces, especially around vessels, due to the presence of edema fluid and cellular infiltration by mononuclear cells.

Several studies of myocardial function have been carried out in animal models with somewhat conflicting results. Total blood volume, red blood cell volume, and cardiac output declined progressively and were proportional to the decline in total body weight in all series. In dogs with PEM associated with atrophy of myofibers and interstitial edema, left ventricular systolic function was depressed at high filling pressures and ventricular compliance decreased (22).

Myocardial performance has also been shown to be depressed in the rabbit model subjected to 6 weeks of protein depletion (23). Protein depletion produced a reduction in total cardiac mass due to decreased nitrogen and glycogen content, while there was an increase in fat content. When compared with other organs, cardiac muscle appears to play a role in energy metabolism similar to that observed in liver and skeletal muscle by undergoing glycogenolysis and proteolysis.

Cardiac function was studied in the isolated rat heart by Freund and Holroyde (24). After 6 weeks of protein depletion, the rats lost 12.8% in heart weight as compared with 14.3% reduction in total body weight. These losses were restored after refeeding. Myocardial developed force and force-velocity were studied using a Langendorff isolated heart perfusion apparatus. Values for these variables were less than for controls and returned to control levels after refeeding.

In the absence of myocardial edema, the rat heart also evidenced bradycardia, systemic hypotension, and a diminished cardiac output (25). When output was adjusted for total body mass, however, the cardiac output index was normal. Furthermore, ventricular function curves failed to demonstrate a loss of myocardial reserve.

Additional studies by the same group did not uncover any decrease in myocardial "stiffness" (25). Ventricular contractility in these models was enhanced, while the duration of the contraction was prolonged.

Therefore, it would appear that when a marasmic animal has no myocardial damage or edema, cardiac mechanics are normal, and there is no impairment of contractility. When a hypodynamic circulatory state occurs, it reflects an adaptation to the generalized hypometabolic state, similar to that occurring in humans. When complicating factors are present, such as myocardial edema, anemia, or myofiber damage, changes in contractility and compliance could take place, and signs of cardiac failure may ensue.
The inotropic effects of isoproterenol, phenylephrine, and calcium were studied in the left atria of 5-week-old rats fed a low- or normal-protein diet for 3 weeks (26). Rats maintained on a low-protein diet consumed about half the amount of food eaten by the same rats maintained on a normal protein intake and thus suffered from PEM. Body weight did not increase in PEM, but heart weight adjusted to body weight was slightly increased when compared with normal rats. Atrial resting tension and peak developed tension in response to isoproterenol, phenylephrine, or calcium were not diminished by PEM. The number of α- and β-receptors and the receptor affinity in ventricular membranes were also not reduced by PEM.

The biochemistry and metabolism of the myocardium in PEM have been studied on a few occasions. Nutter et al. (27) analyzed the left ventricular concentration of DNA, protein, collagen, and actomyosin in a rat model. After 6 weeks of protein and energy deprivation, the body weight and cardiac mass decreased proportionately as compared with controls. DNA content, an index of cell number, was found to be greater by 45% in the undernourished hearts, a finding compatible with a greater cell density in the atrophic myocardium. The total cardiac protein/DNA ratio was lower by 30% in the malnourished myocardium as compared with controls, as was the reduction in myofiber diameter. Further studies of left ventricular collagen and actomyosin revealed a 95% increase in ventricular collagen, while actomyosin values were similar to control levels. This latter observation implies that contractile protein per unit of tissue is unchanged in the malnourished heart. Overall, this would confirm the histologic findings of small, tightly packed myofibers surrounded by abundant connective tissue.

There are few data available on myocardial metabolism in PEM. With fasting, the key regulatory enzyme, phosphofructokinase, is inhibited by rising levels of intracellular citrate, a by-product of fatty acid metabolism (28). Fatty acids supply the bulk of myocardial energy requirements in the adult and increase fourfold within 24 hr of starvation. There is, however, only a slight increase in ketone bodies while plasma fatty acid levels are high.

Tissue levels of adenosine triphosphate (ATP) in the myocardium were increased in the malnourished heart, indicating an ample supply of ATP to satisfy myocardial demands (28).

Amino acid metabolism is altered during starvation as well. Alanine yields pyruvate on transamination with α-ketoglutarate, and pyruvate is then converted to glucose or oxidized in the citric acid cycle. In support of this shift are a low myocardial level of alanine and a fall in the alanine/pyruvate equilibrium ratio (28).

Glutamate also enters the citric acid cycle, and there is a similar fall in glutamate/α-ketoglutarate ratio. These shifts in amino acid metabolism from anabolic to oxidative pathways suggest that amino acids may become important myocardial energy sources late in starvation (28).

At the molecular level, myocardial mRNA has been determined in rats, which were starved and deprived of protein (29). During starvation (1–6 days), the extractable amount of microsomal RNA decreased significantly. The extractable amount of mRNA also fell. When a normal energy but protein-deficient diet was fed, the decreases in extractable microsomal RNA and mRNA were quantitatively similar but
CARDIAC CHANGES IN PEM

TABLE 5. The heart in PEM: findings in experimental models

<table>
<thead>
<tr>
<th>Animal</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Rat</td>
<td>Myocardial atrophy, loss of striations, foci of necrosis, interstitial fibrosis and edema</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Decreased cardiac mass, diminished ventricular performance</td>
</tr>
<tr>
<td>Dog</td>
<td>Myofibrillar atrophy, decreased ventricular contractility</td>
</tr>
<tr>
<td>Primate</td>
<td>Early changes—swelling, foci of necrosis, lymphocytic infiltration; late changes—atrophy of muscle fibers, deficiency of myofilaments and mitochondria</td>
</tr>
</tbody>
</table>

slightly less severe. Analysis of the intracellular distribution of cardiac microsomal RNA and mRNA indicated that mRNA did not accumulate in the cytoplasm but was rapidly degraded. During refeeding, mRNA was transported from the nucleus to the cytoplasm and engaged in polyribosome formation. The specific mRNA species coding for the myofibrillar proteins was affected to a similar extent by starvation, protein deprivation, and refeeding.

The various cardiovascular observations in experimental models of PEM are listed in Table 5.

RELATED DEFICIENCY STATES

Potassium Deficiency

The excessive potassium losses that accompany gastroenteritis may have profound effects on myocardial function. Potassium deficiency is associated with muffled heart sounds, decreased systolic function, and cardiac arrhythmias. Myocardial lesions secondary to hypokalemia have also been described (30). These consist of infiltration by neutrophils, lymphocytes, and macrophages associated with necrosis of myofibers.

The electrocardiographic changes that accompany hypokalemia include prolongation of the QT-U interval, broadening and lowering of the T waves, and prominent U waves. Voltages are generally diminished.

Magnesium Deficiency

A deficiency of magnesium can develop in any child who suffers prolonged losses of body fluids (31). Many of the findings in magnesium deficiency are also found
when serum calcium is low, when hypocalcemia and hypomagnesemia occur together. Signs attributed to magnesium deficiency include impaired circulation with decreased peripheral arterial pulsations, accompanied by tremors, twitching, and possible seizures.

The electrocardiographic findings in magnesium deficiency include unstable heart rate and rhythm with ectopy, low-amplitude complexes, and progressive inversion of the T waves. In the therapy of PEM, magnesium supplementation should be included in the parenteral fluids, because of the slow and incomplete oral absorption of this ion. With magnesium supplementation, the electrocardiogram tends to normalize more rapidly (31).

Selenium Deficiency

Selenium is an essential component of the enzyme glutathione peroxidase. This enzyme protects the cells against oxidative damage by maintaining stability of mitochondrial membranes. Experimental selenium deficiency in the monkey has resulted in degeneration and necrosis of cardiac muscle (32). Keshan disease in China, a necrotizing cardiomyopathy, is believed to be due to a chronic selenium deficiency (33). Children with this disease develop heart failure, with a mortality rate in the range of 50%. Provision of selenium in the diet appears to be protective.

CARDIOVASCULAR COMPLICATIONS OF THE TREATMENT OF PEM

Infants and children with PEM appear to be at high risk of developing cardiac abnormalities during the recovery phase (1,5,7). Congestive symptoms usually develop during the first week of therapy, at a time when fluid and electrolyte disturbances, infections, and anemia are common. In a few cases, sudden death occurs, probably from a lethal cardiac arrhythmia engendered by rapid fluid and electrolyte shifts. In the series of Smythe et al. (5), 13 of 98 infants with PEM died. These authors felt that hypervolemia associated with the mobilization of edema fluid and severe anemia imposed an excessive load on the atrophic myocardium. The series reported by Wharton et al. (7,34) also included a large number of cases of heart failure during recovery. These were associated with a high salt intake. Congestive failure was less frequent when sodium intake was restricted. High doses of milk protein also appeared to provoke signs of congestive heart failure, with a dramatic improvement in clinical status consequent to lowering protein intake, restricting salt content of the diet, and use of diuretics (35).

The metabolic response to treatment is dependent on associated infectious processes, which raise energy demands. A hypermetabolic state certainly takes place during recovery and is accompanied by an increase in heart rate, blood pressure, and cardiac output (36). Cardiac size as determined by CT ratio increases, particularly during the first week of therapy (5).
CARDIAC CHANGES IN PEM

TABLE 6. Cardiovascular events during recovery from PEM

<table>
<thead>
<tr>
<th>First week</th>
<th>Later</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
<td>&quot;Hyperkinetic circulatory state&quot;</td>
</tr>
<tr>
<td>Excessive loading of atrophic myocardium</td>
<td>Increased cardiac output</td>
</tr>
<tr>
<td>Infection</td>
<td>Shortened circulation time</td>
</tr>
<tr>
<td>Anemia</td>
<td>Lower vascular resistance</td>
</tr>
<tr>
<td>Fluid and electrolyte disturbances</td>
<td>Narrow arteriovenous oxygen difference</td>
</tr>
<tr>
<td>Protein loading</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
</tr>
<tr>
<td>Conduction disturbances secondary to sudden shifts in fluid and electrolytes</td>
<td></td>
</tr>
<tr>
<td>Increased cardiac size</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac function during recovery has been studied by a few investigators. Alleyne (37) determined cardiac output using an indicator dilution method and found values that exceeded age-matched controls. This author felt that these findings were a reflection of an increase in total body metabolism as "catch-up" growth took place.

Cardiac catheterization by Viart (17,38) revealed a short circulation time, low vascular resistance, and a narrow arteriovenous oxygen content difference in recovering patients. These findings were supportive of a state of raised cardiac output accompanying the increased metabolic and myocardial demands.

Echocardiographic assessment also confirmed an enlarging cardiac mass, normal systolic function, and an increase in cardiac output in patients during the recovery phase (14,15).

The cardiovascular events that may take place during replacement therapy are cited in Table 6.

FUTURE RESEARCH

With few exceptions, fundamental research related to cardiovascular problems associated with PEM has focused on the mature animal model. Since there are well-defined differences in cardiac structure, myocardial mechanics, myocardial metabolism, response to loading conditions, and autonomic control between the developing and mature myocardium, future studies should be directed toward the disease as expressed in the growing mammal. This could take the form of ultrastructural studies of the disease process, myocardial metabolism, cardiac mechanics, responses to volume loading, afterloading, heart rate and changes in the inotropic state, and the
assessment of therapeutic interventions on the contractile and electrophysiologic status.

At the molecular level, studies should be carried out to assess possible alterations in the contractile proteins, e.g., myosin heavy chains, as PEM develops.

At the clinical level, echocardiographic investigations of cardiac dimensions and systolic and diastolic function should be pursued, incorporating a larger volume of case material. This should include serial determinations performed during the active disease process and during the recovery phase.

REFERENCES

DISCUSSION

Dr. Suskind: Since thiamine is a water-soluble vitamin and, therefore, not stored, how often do these children go into congestive failure as a result of undiagnosed beriberi?

Dr. Talner: Beriberi heart disease, which is associated with a high output state, does not seem to occur in protein-energy malnutrition (PEM).

Dr. Suskind: What about the question of congestive failure?

Dr. Talner: It would be very difficult to relate the congestive heart failure to thiamine deficiency. My own concept is that congestive heart failure in these patients is the end result of abnormal loading of an underloaded myocardium with fluid, proteins, and calories.

Dr. Haschke: The typical clinical finding related to selenium deficiency is a cardiomyopathy. The question is whether the cardiomyopathy is related to PEM or to the selenium deficiency. Do you know if malnutrition were present in those cases reported in China?

Dr. Talner: Experience in selenium deficiency indicates that patients developed a dilated congestive cardiomyopathy. This is not what we see in kwashiorkor, where there might be trace deficiencies of selenium but without producing the same clinical picture.

I should expect the picture of selenium deficiency, such as in China, to produce a dilated, poorly contracting heart similar to the chronic congestive cardiomyopathy that one sees following viral myocarditis, although this cardiomyopathy is obviously correctable by providing selenium. It is also similar, perhaps, to carnitine deficiency, in which there is a dilated heart with decreased contractility, which disappears when carnitine is provided.

Dr. Aggett: My understanding is that children who develop a selenium-responsive cardiomyopathy grow, essentially, at a normal rate.

It is not clear if the myopathy is the result of selenium deficiency alone or a consequence
of associated deficiencies or stresses. There is increasing interest in the use of vitamin E supplementation for management and a renewed interest in the use of vitamin C, which had been commonly used before documentation of the effects of selenium deficiency.

Regarding the reports of patients on parenteral nutrition who had developed selenium-responsive cardiomyopathies, or had died with a possible selenium deficiency, most of these were individuals who had been on prolonged intravenous feeding and had other nutritional imbalances, for example, vitamin E deficiency, where a high-polyunsaturated fatty acid supply, etc., may have predisposed them to the problem.

The question of whether isolated or combined deficiencies contribute to the cardiomyopathy of malnutrition has not been adequately explored.

Dr. Jackson: I should be cautious about saying that it does not happen. Certainly, Golden et al. (1) have suggested that children with decreased selenium status, as measured by the activity of glutathione peroxidase, have evidence of cardiopulmonary failure with an increase in the cardiothoracic ratio. We have seen children in high output cardiac failure, with no urine flow, who responded to thiamine within 5 hr with a diuresis.

There are other variables that have to be considered in the expression of the disease state, such as the carbohydrate load. Measurements of transketolase activity are sufficiently abnormal for one to adopt a cautious approach. Perhaps one of the reasons that overt clinical syndromes are not seen more frequently is that most therapeutic regimens provide generous supplements of vitamins prophylactically.

Dr. Talner: I did not mean to imply that this could not happen, just that the findings in those patients are not what one expects in a high-output state, with the congestive heart failure that is seen in beriberi.

Dr. Gordillo: We had severely malnourished children who presented with dehydration and a serum osmolarity as low as 250 mOsm/kg. When we attempted to correct this with intravenous sodium chloride, by either isotonic or hypertonic infusions, the patients went into cardiac failure. Thus, we learned that extracellular hypotonicity is a chronic disturbance that should be corrected slowly along with the nutritional replacement.

Dr. Okeahialam: Although some deaths from cardiac failure occur after recovery, we are acutely aware of the increased mortality in children with kwashiorkor during the first week as a result of pulmonary edema. What do you recommend as the ideal management, during this period, for the child with kwashiorkor who is in cardiac failure?

Dr. Talner: Since I have not dealt with primarily malnourished children, I should like to present an educated speculation. I think a patient in shock has to be treated by replacing enough volume to restore vital organ perfusion, particularly of the myocardium and the central nervous system. Once intravascular volume has been repleted, one would tend to go slowly, in the hope that fluid can be mobilized.

Caution must be exercised in the use of digitalis, because of the potassium, calcium, and magnesium deficiencies. Various glycosides have been used, and I think they might be appropriate if particular attention is paid to electrolyte abnormalities.

Dr. Suskind: In your review of the literature, were you able to find significant differences in cardiac function between children with marasmus and kwashiorkor? It would also be interesting to know how often cardiologists in the United States, and other countries in which PEM is uncommon, see undiagnosed cardiomyopathies that may be secondary to a specific nutrient deficiency.

Dr. Talner: The recent findings showing a possible relationship between carnitine deficiency and cardiac performance, as well as the correction of the myocardial process with carnitine supplementation, are exciting. There are probably other nutritional deficiencies and
mitochondrial defects to be uncovered that also relate to myocardium metabolism. We know nothing about myocardium metabolism in PEM and little in the developing human. I think this is an area for future research.

Dr. Ballabriga mentioned that the fetus uses carbohydrate as its metabolic fuel and cannot use fatty acids. The adult heart uses fatty acids primarily and uses carbohydrate metabolically as its major substrate under hypoxic conditions.

Regarding differences in cardiac performance between marasmus and kwashiorkor, the only studies I am aware of indicate that when there is myocardial edema, the volume pressure relationship of the myocardium would have to be disturbed. Animal studies have shown some decrease in ventricular compliance.

Dr. Keusch: We found an increased mortality rate among malnourished children even at an excellent metabolic unit like The Institute of Nutrition of Central America and Panama (INCAP) in Guatemala, largely as a result of gram-negative bacteremia. Since this is conditioned by the significant complement deficiency in PEM, and its decreased activity for gram-negative organisms via defects in the alternative pathway, we attempted replacing complement activity by giving intravenous plasma. As a control, we provided other plasma proteins several hours for 3 days, reducing oral protein intake to correspond to the intravenous protein load. Although we had been concerned about putting these children into pulmonary edema, that did not happen. On the fourth day, when dietary intake approximated 4 g of protein per kilo, there were still no cardiac or fluid problems. We also demonstrated that complement activity and opsonic activity could be raised for test bacteria. However, the study was too small to demonstrate that there was, in fact, a protective effect against gram-negative sepsis.

Dr. Talner: Where replenishment has not been overly aggressive, there have been relatively few cardiac complications. I think too aggressive therapy, particularly in the first few days, with a background of fluid and electrolyte abnormalities may be detrimental in the long run.

Regarding the role of infection, I think when a patient has gram-negative infection, there is a great possibility that cardiac performance will be compromised. There is, for example, the problem of fever's increasing oxygen demands in a patient who is in a low metabolic state. We have also seen the effect of infections such as meningococemia and Hemophilus influenza sepsis, where cardiac as well as circulatory performance has been impaired.

Dr. Truswell: Brown atrophy of the heart used to be the standard pathologic description of adults dying of starvation. Do you find this in marasmus? Has there ever been a paper on the pathologic anatomy of the heart in marasmus?

Dr. Talner: Yes, there have been papers that have reviewed the pathology of marasmus and kwashiorkor. Brown atrophy has not been described in PEM.

Dr. Pudjiadi: The first week of realimentation is a dangerous time for the kwashiorkor child. Often the child looks better but dies suddenly during the night. Is this most likely due to cardiac failure?

Dr. Talner: Sudden death usually results from a cardiac arrhythmia. Congestive heart failure does not kill immediately. It develops over a period of hours or days. If it occurs suddenly, then other causes, such as rhythm disturbances or acute airway obstruction, should be considered. The pathologic picture of myocardial atrophy, lesions of the conduction system, and rapid changes in serum electrolytes could account for potentially lethal cardiac rhythm disturbances.

Dr. Suskind: The treatment of severe anemia by transfusion can place the child at risk of developing congestive failure. In those cases, we found that the use of magnesium made a difference in terms of the reversing cardiac failure.
Dr. Talner: Caddell's work on magnesium supplementation was a significant contribution in the management of these patients.

In regard to raising oxygen transport by blood transfusions, it is important to remember that the decrease in hemoglobin developed over a long period of time and does not have to be corrected rapidly. A satisfactory level of oxygen transport should be reached after which one can move more slowly. Digoxin administration may provide a means to maintain myocardial performance as the anemia is being corrected.

Dr. Suskind: These were children who often had hemoglobins of 3 to 4 g/100 ml.

Dr. Talner: They do not have to reach 12 g/dl over a few hours.

Dr. Brunser: From the point of view of fine structure, the changes seen in the heart are similar to those observed in striated muscle. The discoloration in the myocardium referred to as brown atrophy is probably due to two factors. One is the accumulation of residual bodies, which contain a pigment called lipofuscin, and the other is that mitochondria are brownish. As the muscle fibers decrease in size, the proportion between mitochondria and myofibrils increases, and the heart acquires the brown color that characterizes this type of lesion.

REFERENCE