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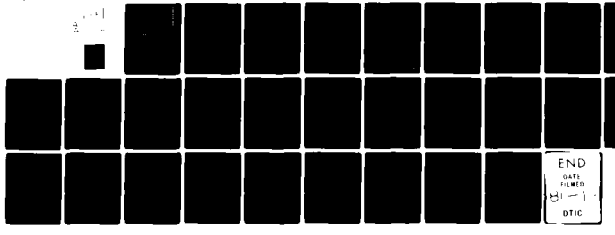

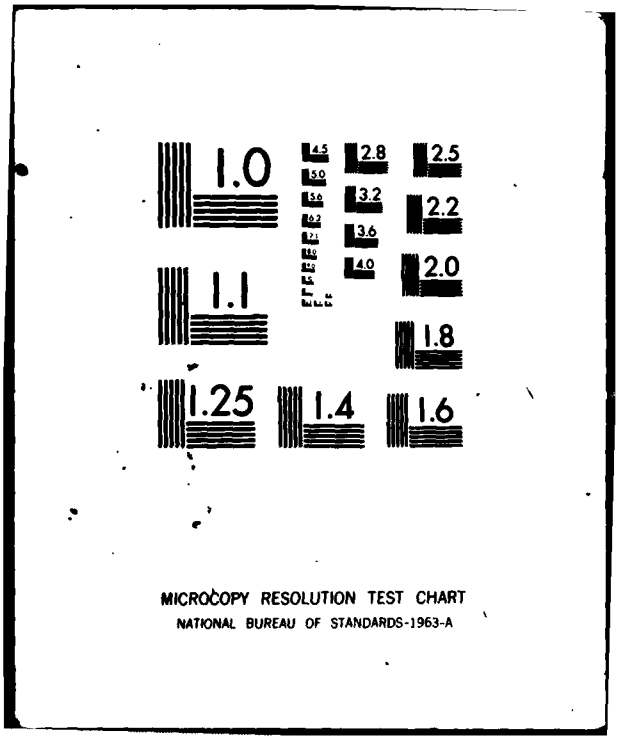
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This brief review describes the generalized metabolic and nutritional events that occur during febrile infectious diseases in man, and outlines the clinical approaches that should be followed for providing supportive therapy during and after the illness.

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IV. 1. 2. INFECTION

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a. Overview

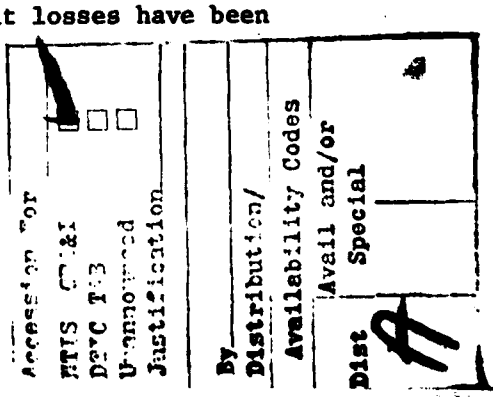
Infectious illnesses stimulate a complex array of metabolic and nutritional responses. These responses support generalized and antigen-specific immunological defensive mechanisms and help to supply the broad demands of body cells for the increased quantities of energy-generating substrates needed during periods of fever, infection-induced stress, and tissue repair (1).

The magnitude and type of nutritional losses caused by an infection reflect both the severity and duration of an illness. Nutritional losses are influenced additionally by the generalized or localized nature of a given infectious process, by the age, sex, and pre-illness nutritional status of the patient, as well as by the possible presence of underlying or complicating medical or surgical diseases.

Despite the complexity of the interrelated biochemical, metabolic, endocrine, and nutritional responses to infection, these responses develop and eventually regress in an orderly, predictable sequence which appear to be related to the evolving phases of the infectious process. An improved understanding of the fundamental cellular response mechanisms at play during the course of an infection should allow the thoughtful physician to anticipate probable nutritional deficits and plan the most appropriate measures for supportive care.

b. Identification of Nutrient Needs

In attempting to define nutrient needs of a patient who suffers from an infectious illness, it is necessary to know which nutrients are influenced by the disease process. Two broad types of nutrient losses have been identified, absolute and functional.



(1) Absolute nutrient losses

The most conspicuous nutritional consequence of an infectious illness is an absolute (i.e. measurable) loss of body constituents (1). This is reflected clinically by a loss of body weight and muscle tone, and by the progressive wastage of muscle mass and body fat. These losses are associated with negative body balances of the principal intracellular elements during generalized infections, including nitrogen, potassium, magnesium, phosphorus, zinc, and sulfur (1, 2). Absolute losses of nitrogen may vary from 20 to 90 g, with the losses of the other intracellular elements being proportional to those of nitrogen (2). If an infection is characterized by massive diarrhea and vomiting, absolute losses of body water, sodium and chloride may become life threatening. Diarrhea-induced fecal losses of bicarbonate and potassium ions may induce additional problems in acid-base balance. Some infections also cause absolute losses of body protein and red blood cells.

(2) Functional nutrient losses

In addition to the absolute, or direct losses of body nutrients, several functional forms of nutrient loss must be anticipated. Functional losses are defined as the within-body losses of nutrients due to infection-induced metabolic or pathophysiologic responses. These functional loss categories include an increased utilization, diversion, or temporary sequestration of nutrients. Functional losses may progress to absolute losses.

As examples, metabolic rates increase about 7% for each F^{o} degree increase in body temperature. Since these extra energy requirements are typically met through an accelerated cellular utilization of carbohydrate, the rate of gluconeogenesis must be increased also. This process diverts both

essential and nonessential amino acids from other uses, and, together with accelerated ureagenesis, helps to account for some of the direct losses of body nitrogen. Sizeable amounts of tryptophan may be diverted into the kynurenine pathway during some infections, especially typhoid fever, and tryptophan metabolites then appear in the urine as diazo reactants. An increased metabolic utilization of vitamins must also be anticipated during infections (1).

Another of the functional forms of nutrient loss during infection occurs as a redistribution of certain body electrolytes and minerals. Iron and zinc are rapidly sequestered in storage forms by hepatic cells; in contrast, copper is secreted by the liver as a component of ceruloplasmin. In infections of marked severity, sodium may be reduced in the extracellular fluids and accumulate within body cells.

c. Infection-induced Anorexia

Acute febrile illnesses are generally accompanied by anorexia, nausea, and sometimes by vomiting. These gastrointestinal symptoms have not been explained by any clearly defined mechanism, although they may be of central nervous system origin. It is equally uncertain if infection-induced anorexia serves the host in a purposeful manner and should therefore be classified as a generalized defensive measure (3).

(1) Consequences of anorexia

Nevertheless, anorexia reduces the intake of food appreciably, even to the point of total abstinence during days of high fever. The diminished intake of food contributes to the negative balances of body nutrients during fever. However, the febrile losses of body nutrients

are far greater than can be accounted for by anorexia. Hypermetabolic consequences of fever appear to prevent the homeostatic mechanisms normally used by the body as nitrogen-sparing devices during periods of uncomplicated starvation or semistarvation.

(2) Other gastrointestinal functions

In addition to anorexia and disturbed gut motility, generalized infections alter rates of intestinal mucosal cell replication and maturation, and some (such as measles) can cause protein-losing enteropathy.

Pathogenic enteric microorganisms may cause lesions within the mucosa, intestinal wall and lymphatics which interfere with absorptive functions. Parasites can also cause intestinal losses of blood cells and protein. If their total mass becomes sufficiently great, parasites compete with mucosal cells for dietary nutrients. Alterations in the number, composition, and location of intestinal microflora can result from antibiotics or purgative therapy. All of these changes, along with the effects of microbial enterotoxins, may interfere with nutrient absorption (1).

d. Nutritional Responses to Infectious Illnesses

When virulent microorganisms penetrate host defenses, a sequence of nutritionally important events evolves in a relatively predictable manner. Nutritional costs of illness are related to the severity and duration of illness, the occurrence of certain complications, or the localization of the infection in a single organ system. Although the type of infecting microorganism will influence the nutritional response to some degree, the overall patterns of nutritional loss are quite similar, or stereotyped,

despite organism-to-organism differences (2).

(1) Acute febrile illnesses

The variety of nutritional responses during a generalized infection is broad enough to include most major metabolic pathways of body cells. Alterations may occur in rates of protein synthesis and degradation, in the metabolic processing of individual amino acids and other nutrients including electrolytes, minerals, trace elements, and vitamins, and in the production and utilization of cellular energy. Many of these responses are regulated by hormones or other biologically active substances released from body cells. The responses are also influenced by the presence of fever, the availability of key nutrients derived from body stores or from the diet, and any nutrient losses caused directly by microorganism uptake.

(a) Catabolic losses

Sharply negative balances of body nitrogen begin soon after the onset of fever. Nitrogen losses via the urine exceed dietary intake values, and occur in the form of urea, ammonia, creatinine, alpha-amino nitrogen, and sometimes of creatine, diazo reactants, and uric acid (2). An increased excretion of 3-methylhistidine indicates that a major portion of lost nitrogen is derived from protein components of skeletal muscle. Nitrogen may also be lost in sweat, but fecal losses do not generally increase unless diarrhea is present.

The patterns of nitrogen loss typify the proportional losses of other principal intracellular elements. During periods of rising fever, hyperventilation-induced respiratory alkalosis leads to a

transient decrease in urinary phosphate loss, but thereafter, phosphate losses reflect those of nitrogen. Calcium, on the other hand, is not generally lost unless muscle paralysis supervenes, as in poliomyelitis. In a paralytic infection, prolonged loss of body calcium, ascribed to disuse atrophy of bone, is accompanied by phosphate losses from bone as well as from muscle.

(b) Fluid and electrolyte losses

In most forms of infection, the major extracellular electrolytes, sodium and chloride, are influenced more by hormonal events than by changes in dietary intake. However, infection-induced changes in salt and water homeostasis can reach a life-threatening extreme at either end of the spectrum, i.e., severe dehydration or fluid overload.

A brief period at the onset of a generalized symptomatic infection may be accompanied by an increased urinary excretion of sodium and chloride. Salt will also be lost via sweat if diaphoresis is an important component of an infection.

If diarrhea should occur, direct fecal losses of sodium, chloride, bicarbonate, and potassium result. Body losses of chloride and hydrogen ions can also be sizeable if vomiting becomes excessive during an infection.

Despite these possibilities for acute losses of body salt, most severe generalized infections lead to saline and water retention. Initial brief renal losses do not persist. Rather, within a day or so after the onset of fever the kidney begins to retain sodium and chloride. This renal conservation of electrolytes is brought about, in part, by increased secretion of adrenal mineralocorticoids. Retention of salt is often accompanied by retention of body water, sometimes to the point of dilutional hyponatremia. With a successful

cure of a severe illness, excess accumulated body water is typically lost by diuresis in early convalescence (1).

Severe retention of body water, especially during central nervous system infection, has now been widely ascribed to an inappropriate secretion of antidiuretic hormone from the posterior pituitary gland (4). In addition, in some severe infections, membrane transport functions of cells are disturbed in a manner that allows sodium to accumulate intracellularly.

(c) Acid-base balance

Pathogenic mechanisms that come into play during various infections can lead to metabolic alkalosis or acidosis, to respiratory alkalosis or acidosis, or to complex admixtures of these perturbations.

The onset of fever is typically accompanied by tachypnea and accelerated respiratory gas exchange, an exaggerated loss of CO_2, and a state of uncompensated respiratory alkalosis. Alkalosis may persist as long as febrile tachypnea lasts and gas exchange within the alveoli remains unimpeded. Conversely, infections that cause pulmonary consolidation can impair CO_2 exchange and lead to respiratory acidosis. Respiratory acidosis also develops if pulmonary musculature can no longer function effectively, as in poliomyelitis or tetanus.

Metabolic acidosis is seen whenever an infectious disease becomes extremely severe. With hypotension, vascular stasis, and cellular anoxia during gram-negative sepsis, for example, the generation of excess lactic acid and other metabolic acids exceeds the capacity of body buffering systems.

Diarrheal diseases can be accompanied by two additional forms of metabolic acid-base derangement. Diarrhea characterized by extremely high-volume stool losses, as in Asiatic cholera, causes an excessive loss of

bicarbonate in the stool with a resultant decline in blood pH. Bicarbonate is actively secreted in the lower ileum and cannot be completely reabsorbed by the colonic mucosa if there are high-volume losses of watery stool. In contrast, diarrhea accompanied by only low-volume stool losses tends to be associated with an exaggerated loss of fecal potassium rather than bicarbonate. If fecal potassium losses persist chronically over a long period of time or occur rapidly during massive acute diarrhea, body stores can be severely depleted. Loss of cellular potassium leads to metabolic alkalosis.

(d) Trace element nutrition

Plasma concentrations of iron and zinc decline abruptly with the onset of fever. These phenomena are due to an accelerated uptake by the liver of both iron and zinc. The iron accumulates in granules as hemosiderin or ferritin complexes. Iron is not readily released from these storage forms as long as infection persists. The abrupt decline in plasma iron is most marked in pyogenic bacterial infection, but has been noted in viral infections as well. The movement of iron into the liver is not initially accompanied by a reduction in plasma iron-binding capacity, and, as a result, the percentage of unbound plasma transferrin increases. This increase in unsaturated transferrin is thought to be of positive benefit as a host defensive mechanism, for it serves to minimize the availability of iron needed to permit replication of some invading microorganisms (1). Accumulation of iron in storage depots is accompanied by an increase in plasma ferritin values; this increase has diagnostic value and serves to differentiate infection-induced changes in iron metabolism from iron-deficiency anemia, where plasma ferritin values are low.

The decline in plasma zinc is not as marked as that of iron, but, like iron, zinc is also taken up by the liver. The liver does not normally have an ability to store zinc; however, acute infectious or inflammatory processes activate phagocytic cells to release endogenous mediating substances (5) which, in turn, stimulate hepatocytes to initiate a rapid synthesis of metallothionein proteins. The newly formed hepatic metallothioneins, with their unusually large number of sulfhydryl groups per molecule, are able to bind large quantities of zinc and to retain this element within the liver until the infectious process is terminated.

In addition to the redistribution of zinc within the body, overall zinc balances become negative because of a combination of factors, including reduced dietary zinc intake, increased losses via the urine, and possibly via the feces and sweat as well. During acute infectious hepatitis there is an unusually large loss of zinc via the urine. This has been ascribed to an increase in the percentage of plasma zinc which is bound in the form of a microligand to the amino acids, histidine and cysteine. The small size of these zinc microligands permits them to pass through the renal glomerulus.

Plasma concentrations of copper begin to increase shortly after the onset of fever. This is the result of accelerated hepatic synthesis of ceruloplasmin, the copper-binding protein of plasma. Ceruloplasmin values remain elevated during infection and then begin a gradual return to normal with the onset of convalescence.

(e) Vitamin metabolism

Plasma concentrations of some of the vitamins may decline during acute infections; negative balances of nitrogen may be accompanied by an

increased urinary loss of riboflavin (1). B-group vitamins, folate, and ascorbic acid all participate in the heightened cellular metabolism seen whenever phagocytic cells become activated. The B-group vitamins also participate in the replication and functional activities of lymphoid series cells. The rapid production of adrenocortical hormones during infection causes the vitamin C content of the adrenal gland to decline abruptly. Vitamins A and E also appear to be of value in maintaining the competence of normal host defense measures (1).

The intestinal absorption of fat-soluble vitamins and folate may be impaired during enteric infections or parasitic infestations. Parasites with a large bulk, such as tapeworms, may take up enough B-group vitamins from intestinal lumen fluids to produce deficiency states in the host.

Although little is yet known about alterations of vitamin metabolism at the molecular level, severe acute infections can, on occasion, precipitate acute avitaminoses, including scurvy, beriberi, pellagra or night blindness.

(f) Protein metabolism

Acute infections trigger a unique admixture of concomitantly accelerated anabolic and catabolic effects on protein metabolism (1). The contractile proteins of skeletal muscle and other proteins of somatic tissues of normally nourished persons appear to provide an available pool of labile body ntirogen. The accelerated catabolism of these proteins during acute infection generates free amino acids for use in the synthesis of other kinds of protein or for diversion into energy-yielding processes.

Liver cells take up free amino acids at an accelerated rate during acute infections. The avidity of the liver for amino acids is sufficiently great during early infections that their uptake exceeds their rate of release from degraded body proteins. This causes the concentrations of most free amino acids in plasma to decline. Amino acids entering the liver are used for the accelerated de novo synthesis of hepatic proteins or for gluconeogenesis. On the other hand, neither tryptophan nor phenylalanine can be utilized as rapidly as they are released during the catabolism of somatic proteins. Tryptophan excesses appear to be managed within the liver by shunting them into either the serotonin or kynurenine pathways. Excess phenylalanine accumulates for a time within the plasma in coincidence with an accelerated utilization of tyrosine. Thus, the plasma phenylalanine:tyrosine ratio increases during acute infectious illnesses. In infections of overwhelming severity, the liver can no longer take up and metabolize free amino acids as rapidly as they are released, and a preterminal period of hyperaminoacidemia may develop.

Every host defensive measure is ultimately dependent upon the ability of body cells to synthesize new proteins. Protein anabolism is important for the production of new phagocytes, lymphocytes, and antibody-producing plasma cells. Interaction of neutrophils and macrophages with microbial pathogens or necrotic debris leads to the synthesis and release into plasma of cellular proteins including lactoferrin, lysozyme, endogenous pyrogen and other mediators (5). The lymphocytes produce proteins such as interferon and the lymphokines. Fibroblasts produce cold-insoluble globulin; endocrine organs secrete polypeptide hormones in increased amounts, including ACTH, growth hormone, insulin, and glucagon.

At the same time, the liver accelerates its synthesis of many proteins while slowing the production of albumin and transferrin. The accelerated or de novo synthesis of hepatic proteins includes a number of enzymes, metallothioneins, complement, kinin, coagulation system components, lipoproteins, and acute-phase reactant plasma proteins. This latter group includes haptoglobin, $alpha_1$-antitrypsin, C-reactive protein, $alpha_1$-acid glycoprotein (orosomucoid), ceruloplasmin, and fibrinogen (1).

(g) Carbohydrate metabolism

During periods of febrile illness the additional metabolizable energy needed by body cells is provided largely by glucose (6). Hormonal mechanisms and substrate availability contribute to an increased hepatic output of glucose. Although some glucose is derived from glycogen, most comes from gluconeogenesis. Recycled lactate and gluconeogenic amino acids (alanine and glycine) are the principal substrates used by the liver, while pyruvate and glycerol also contribute.

If the ability of the body to sustain the increased rate of glucose production should fail, hypoglycemia may emerge as an important clinical problem. Infection-induced hypoglycemia generally results from one of two pathogenic mechanisms, i.e., a diminished availability of substrate or a failure of hepatocellular competency. Hypoglycemia in septic newborn infants is generally due to a lack of substrate, while the hypoglycemia associated with severe hepatitis serves to illustrate the breakdown of cellular gluconeogenic mechanisms (1, 6).

(h) Lipid metabolism

Changes in lipid metabolism during the course of infection are far more difficult to understand than are those of carbohydrate and protein (1, 6). Plasma cholesterol values increase in some infections and decrease in others. Free fatty acids, which are transported in plasma through their binding to albumin, are generally reduced in concentration. Triglycerides, on the other hand, may accumulate in plasma in amounts sufficient to give it a creamy appearance. Such hyperlipidemia is most characteristic in severe gram-negative sepsis. Hypertriglyceridemia results from an increase in hepatic synthesis in combination with diminished activity of lipolytic enzymes in peripheral tissues.

The metabolic needs for extra energy during periods of acute fever are largely met by the oxidation of glucose and branched-chain amino acids. In contrast, fat depots do not appear to contribute more energy substrates than they generally yield under basal fasting conditions.

The hepatic conversion of free fatty acids to ketone bodies within the liver contributes importantly to body energy needs during periods of simple starvation. This mechanism normally serves to "spare" or conserve body proteins during starvation. However, the capacity of the liver to synthesize ketones is not fully utilized during acute infectious illnesses (6). The mechanisms responsible for inhibition of ketogenesis during infection are not fully known, but since pancreatic insulin secretion increases during fever, the antiketogenic effects of insulin may be playing a role. The lipogenic effects of insulin may also contribute to enhanced hepatic synthesis of fatty acids. This increase in the production of fatty acids helps to explain

fatty metamorphosis of liver cells during severe acute infections as well.

(2) Subacute and chronic infections

If an infectious process becomes subacute or chronic, metabolic functions of the body tend to reach new equilibrium settings. Concentrations of plasma albumin and transferrin begin to decline. In some subacute infections, iron concentrations in plasma may increase to values greater than normal. This has been noted during the second and third weeks of hepatitis and during late stages of typhoid fever.

The adrenocortical production of glucocorticoid and ketosteroid hormones often declines into a subnormal range. The labile pool of body nitrogen is depleted progressively and nitrogen balance enters into a precarious new steady state, but at a cachectic level. Body fat depots also become depleted slowly, and generalized protein-energy malnutrition may ensue. A similar state can emerge as an end result of a series of closely spaced acute infections. This gives rise to the concept that infection and malnutrition may interact to produce a vicious cycle or downhill spiral (1). In this regard, it is unusual for chronic severe malnutrition to exist in the absence of a superimposed or coexisting infectious complication.

Chronic infections, accompanied by protein-energy malnutrition are also characterized by impairment of host defensive mechanisms and immune system competence. Functional anergy of nutritional origin involves both the cellular and humoral arms of the immune system, but, fortunately, this defect can generally be reversed by correcting the nutritional deficits and curing the infection.

Patients subjected to severe starvation or protein-energy malnutrition may not manifest the expected typical signs of infection. They may be unable to mount a fever, produce a leukocytic or inflammatory response, or generate a granulomatous reaction. For these reasons, the nutritional rehabilitation of a severely malnourished patient may allow the emergence of a clinically inapparent infection. A refeeding program may thus become complicated by the sudden appearance of a life-threatening infectious illness (3).

(3) The convalescent period

When acute infectious illnesses terminate uneventfully, negative nitrogen balances are promptly reversed. Thus, body nutrient stores generally reach their lowest levels within several days after fever has subsided. Anorexia disappears at the same time as fever in most patients, and appetite is regained. The body then begins to replenish its depleted nutritional stores, although full nutritional recovery may require many weeks. It seems desirable to utilize the early convalescent period following an acute illness to speed up the repletion of lost body nutrients by providing patients with increased quantities of highly nutritious foods. Hyperphagia may stimulate convalescent children to consume about twice their normal daily intake of food until a "catch-up" weight gain restores their weight:height ratios to normal.

On the basis of both metabolic balance studies and measurements of host defensive capabilities (such as phagocytosis) (1, 2), patients would seem highly susceptible to a superimposed new infection during the early states of convalescence. A secondary infection acquired at that critical time may block nutritional recovery, and lead instead to an additional depletion of body nutrients.

e. Specific Recommendation

Far too little is known about optimum techniques for using nutrient therapy as a key supportive measure in the management of infectious disease. The objectives of nutrient management should be to support physiological host defense mechanisms and optimize the ability of the host to recover from illness. This will shorten convalescence and minimize the likelihood of a superimposed secondary infection.

In most acute infectious diseases that develop in a well-nourished person, the illness is relatively brief and the potential value of nutrient supportive therapy is considerably less than the more pressing need to identify the causative microorganism without delay and to initiate appropriate antimicrobial therapy quickly. Dietary measures should thus be used in support of the selected regimen of antimicrobial drugs.

In many of the common brief infectious illnesses, such as the respiratory viral diseases, effective antimicrobial therapy is not generally available, but the infection is likely to be short-lived and relatively mild. Any nutrients consumed during the illness will serve to minimize the anticipated losses of body components. Since cumulative nutrient losses incurred during a mild self-limited viral infection may not be fully reconstituted until after several weeks of convalescence, emphasis should be placed on providing nutrient support during this latter period.

In some acute infectious diseases, especially those associated with severe diarrhea, the need to provide immediate nutrient support in the form of fluid and electrolyte replacement therapy takes precedence over other forms of therapy. In occasional infections, oxygen may become a critical nutrient that must be supplied without delay.

(1) Control of fever

The duration and severity of fever influences the magnitude of both absolute and functional losses of body nutrients. Lessening of fever by antipyretic drugs and by direct physical methods serves to minimize the increased nutritional needs associated with a hypermetabolic state. Control of fever also reduces dermal losses of nutrients via sweat.

Modest elevations of body temperature provide positive benefit during some experimental infections in laboratory animals. Fever may also help to control a few infections in man (such as central nervous system syphilis or localized chronic gonococcal infections). On the other hand, high fever can be dangerous, and, at best, its putative benefits do not outweigh those of an effective antibiotic. Accordingly, the control of fever has positive nutritional value. In any event, the nutritional impact of fever must be taken into account when calculating daily needs for dietary energy and protein.

(2) Estimation of energy requirements

The caloric needs of a patient with an infectious illness include the normal basal dietary allowance plus extra amounts needed because of fever. The extra daily requirements can be calculated according to the amount of fever (7% increase for each ^{o}F of elevation).

Thus, a 27-year-old male weighing 65 kg, who ordinarily requires an energy intake of 2,500 kcal, with a body temperature $3^{o}F$ above normal, would require 2,500 kcal, plus 3 times 7% of 2,500 kcal. This amounts to 2,500 plus 525 kcal, or 3,025 kcal/day. Alternatively, a febrile adult could arbitrarily be given 30-40 kcal/kg/day, a child, 100-150 kcal/kg/day, and an infant, 200 kcal/kg/day as desirable total energy intakes. If the

sick patient cannot consume these calculated quantities of food, decrements should be corrected during convalescence.

The adequacy of energy intake during an extended illness can also be determined by changes in body weight. However, a loss of tissue mass may be masked by the tendency for febrile patients to retain salt and water. The true loss of body weight may not become apparent until early convalescence when postfebrile diuresis causes excessive fluid to be excreted.

(3) Protein requirements

Despite the importance of the protein-synthesizing capabilities of individual cells, the body will sacrifice amino acids through functional diversions to provide for total energy needs. Thus, the protein requirements of a febrile patient will depend in part on the availability of sufficient dietary energy input. It is usually possible to reduce excessive losses of body nitrogen in febrile patients by increasing energy intake.

If energy intake is inadequate, amino acids derived from dietary protein or existing body pools are diverted to meet needs for energy rather than for incorporation into the structure of new proteins or for other metabolic uses unique for each amino acid. Since additional metabolic energy must be expended to deaminate the amino acids used for carbohydrate synthesis, the use of amino acids for calorigenesis is doubly wasteful.

Exact protein requirements have not been determined during fever. However, the nitrogen intake should be increased if possible to about 1.5 g/kg/day for febrile adults and 3.0 g/kg/day for febrile children. The nitrogen source should include a balanced supply of essential amino acids (1).

Several simple alternative methods are available for estimating protein

requirements. Urea nitrogen assays can be performed by most clinical laboratories on 24-hour urine specimens. A daily urea nitrogen excretion value plus 4 g (2 g for nonurea nitrogen in urine and 2 g for stool nitrogen) provides a reasonable estimate of nitrogen loss. If this value is compared with an estimate of nitrogen intake based on food table values, a rough approximation of nitrogen balance can be obtained.

(4) Acid-base stabilization

The clinician must be aware of possible changes in acid-base equilibrium to determine if corrective therapy is required during illness, or replacement therapy during convalescence. Metabolic acidosis during severe diarrhea can be treated by adding bicarbonate or lactate to replacement fluid infusions. Such treatment should be continued until the urine pH becomes alkaline. If potassium losses are great, vacuolar degeneration of body cells may develop, especially in the renal tubules. Hypokalemic metabolic alkalosis can persist for many months unless treated. The development of hypokalemic nephropathy and metabolic alkalosis can be prevented by replacement therapy with potassium, using commercial solutions to provide 20-35 mEq of potassium per liter during severe diarrhea. Any residual or chronic deficit should then be corrected with high-potassium foods given during the convalescent period.

(5) Electrolyte and water requirements

An infectious process may lead to death from divergent types of fluid imbalance which range from severe overload to severe dehydration. Direct losses of salt and water occur in diseases accompanied by massive or protracted diarrhea, vomiting, or marked diaphoresis. In the absence of such direct losses, the body usually retains fluid and electrolytes. With severe illness, sodium may accumulate within poorly functioning cells. Water retention due to

inappropriate antidiuretic hormone secretion will increase the severity of hyponatremia. Appropriate therapy in the latter types of salt and water derangements requires a careful restriction of fluid and electrolyte intake (4). Thus, a patient with infectious illness may have an emergency need for electrolyte replacement or may, on the other hand, be seriously harmed by fluid and electrolyte administration.

(a) Dehydration problems

In massive diarrhea, the watery stools are virtually isoosmotic with plasma. Because stool losses are isoosmotic, water does not move from body cells to maintain the extracellular volume, and an immediate threat to life may emerge due to depletion of circulatory volume. The extent of body dehydration can be assessed by clinical signs, together with high hematocrit values and increased concentrations of total plasma proteins in relationship to plasma water. This type of dehydration increases the specific gravity of both whole blood and plasma. Because plasma proteins may undergo a two-fold increase in concentration during severe cholera, measured sodium and chloride concentrations may appear to be diminished if they are calculated and expressed, conventionally, on the basis of whole plasma values. Electrolyte concentrations in plasma water of such dehydrated patients must be recalculated to reflect the high protein concentration and diminished amount of water present in the plasma.

Isoosmotic dehydration due to massive diarrhea should be corrected by the use of isotonic replacement fluids, given rapidly to correct shock, and to return hematocrit and plasma protein concentrations to normal. After initial rehydration, homeostasis is maintained by infusing i.v. solutions at a rate to match measured hourly stool volume losses. Potassium deficiency

can be made up by mouth or by potassium-containing fluids.

(b) Overhydration problems

Dehydration is not usually a problem in generalized infectious diseases that do not include diarrhea or repeated vomiting. Rather, the onset of fever is typically accompanied by increased secretion of aldosterone and antidiuretic hormone. Acting in concert on distal renal tubular cells, these hormones cause the kidneys to retain both salt and water. Sodium and chloride may virtually disappear from the urine and urine volume may be sharply reduced.

If the secretion of antidiuretic hormone persists in an inappropriate fashion, body water is retained even in the presence of declining plasma concentrations of both sodium and chloride (4). Because of the retention of salt and water in many infectious illnesses, it is generally unwise to administer saline. Further, if chronic metabolic acidosis develops, variable amounts of sodium may accumulate within the body cells. The sequestration of sodium within body cells is evidence of severe illness and is not easily reversed. The unwise i.v. administration of saline in an attempt to correct depressed plasma sodium concentrations in such patients may have serious consequences, such as cerebral edema or congestive heart failure.

Severe hyponatremia that cannot be explained by direct sodium losses should be managed by restricting salt and water intake until after the infectious process is controlled and plasma sodium concentration begins to increase (1, 4). This type of problem is most common in the aged, or in children with central nervous system infections, Rocky Mountain spotted fever, or other severe generalized infections. Daily fluid intake should be severely restricted. Body weight, urinary specific gravity and volume, and

plasma and urine values for sodium and osmolality should be measured each day; central venous pressures may need to be followed in some patients. Only after urinary specific gravity begins to decline and the daily urine volume increases can fluid intake be liberalized.

(6) Mineral and trace element requirements

Little direct information is available about the need to employ minerals or trace elements as therapeutic agents. For the present, the wisest course of action would seem to demand that natural foodstuffs be given, if possible during illness, and certainly during early convalescence.

Magnesium concentrations in serum may decline somewhat as the result of retention of body water. Negative balances of magnesium occur in close proportion to negative balances of nitrogen. Little has been said concerning the use of magnesium supplements in infectious illnesses, but they may be needed if there is a prolonged negative balance of this element.

Calcium concentrations in plasma may also undergo a dilutional decline, but otherwise calcium metabolism does not seem to be influenced importantly by most infectious illnesses. However, body balances of calcium and other bone minerals may become negative if an infectious disease causes body immobilization or paralysis. Calcium accumulates in devitalized tissues, and the tendency for granulomatous tubercular lesions to become calcified is well known. A high calcium intake was employed in the preantibiotic management of tuberculosis, but there is little to suggest that the calcium helped to arrest the disease. On the other hand, tuberculous patients may develop hypercalcemia because of a sarcoidosis-like hypersensitivity to vitamin D; if this occurs, vitamin D and calcium intakes must both be carefully controlled to avoid hypercalcemia.

Unusually low serum concentrations of inorganic phosphate have been reported in patients with gram-negative sepsis and in Reye's syndrome. Reduced plasma phosphate concentrations may serve as a possible diagnostic indicator of sepsis. Plasma phosphate values also decline rapidly but transiently during the early stages of fever, apparently as a secondary manifestation of respiratory alkalosis. Hypophosphatemia during an acute rise in body temperature is accompanied by the virtual disappearance of phosphate from urine and sweat. These changes occur too rapidly to be accounted for by parathyroid gland responses.

Organic phosphate moieties and high energy phosphate bonds undoubtedly contribute at the cellular level to host responses to infection. It is not known how these changes influence the outcome of an infection, and there is no direct evidence that the administration of phosphate as a single nutrient would be of clinical importance.

Iron metabolism is markedly altered by infection. The initial acute decline in plasma iron occurs without appreciable changes in plasma iron-binding capacity. If an infectious process becomes chronic, plasma iron values remain low and iron-binding capacity begins to decline slowly. This infection-induced sequestration of iron in tissue stores, together with a tendency for red blood cell survival to be shorter, can give rise to the so-called "anemia of infection."

During chronic infections, the administration of iron by either oral or parenteral routes is ineffective in reversing the anemia of infection. If parenteral iron therapy is given while an infectious process remains active, the administered iron also becomes sequestered in storage forms. Liver extract,

the folates, or vitamin B_{12} are similarly without value in reversing anemia.

Further, if iron therapy is given to children with kwashiorkor or protein-energy malnutrition, it can have unexpected consequences. The administered iron may saturate the low iron-binding capacity of protein-malnourished children. The presence of saturated transferrin in plasma increases the availability of iron to aerobic and facultative bacterial pathogens. The bacteria may then proliferate rapidly and overwhelm the impaired host defensive mechanisms of the malnourished child. Thus, if total plasma iron-binding capacity is depressed in a malnourished patient, iron therapy should be delayed until after protein repletion measures have restored plasma iron-binding capacity to near-normal values.

Like iron, serum zinc moves rapidly from plasma into the liver during the early stages of most infectious illnesses. This response may be of positive value in terms of host survival, for neutrophilic phagocytosis is enhanced at zinc concentrations slightly lower than those of normal plasma. In addition, as illness progresses, zinc balances can become negative as a result of diminished dietary intake of the metal along with increased losses in urine, feces, and sweat. No data exist to document any potential therapeutic value of excess zinc administration during acute infections. Since body losses of zinc are to be anticipated, foods with a high content of zinc are of value for use during convalescence.

(7) Vitamin requirements

Despite the paucity of detailed information concerning the rate of utilization or metabolic fate of vitamins in body stores during infection, there can be no doubt that vitamins contribute to the competency of various

host responses. Antimicrobial drugs can also influence vitamin metabolism. Isoniazid, for example, has been thought to induce peripheral neuropathy in some tuberculous patients by causing a deficiency of vitamin B_6. Pyridoxine supplementation has therefore been suggested for patients taking isoniazid.

Based on evidence presently available, practicing physicians should employ vitamins in normally recommended doses during a brief infectious illness, or, should increase doses one- or two-fold during more protracted illnesses to cover the increase in vitamin metabolism (or excretion) during hypermetabolic states. Scientific evidence to justify megavitamin therapy in the treatment or prevention of infectious illnesses does not exist.

f. Mode of Meeting Requirements

Infectious diseases are the most common form of illness to afflict mankind. Most humans experience numerous bouts of infection during a lifetime. Secondary infections can develop to complicate therapy during virtually every other form of illness. There are relatively few instances in clinical medicine where nutritional modalities of therapy are of specific direct importance in managing an immediate life-threatening infection. However, these situations must be recognized quickly and treated effectively when they occur. Perhaps the best example of such an emergency requirement is the need to correct the massive loss of body fluids and electrolytes that occur during fulminant diarrhea. Acute nutritional imbalances may also occur in infections that damage key body cells, deplete key body nutrients or allow toxic metabolites to accumulate. If severe, infectious hepatitis may produce hypoglycemia or hepatic failure. Severe hypoglycemia is also a common danger in neonatal

infants with sepsis. Life-threatening hypoglycemic shock can be suspected through clinical signs, diagnosed by blood glucose analysis, and corrected with glucose infusions.

In contrast to the infrequent requirement for emergency nutritional intervention, most acute infectious illnesses can be managed without the need for aggressive nutritional therapy. Anorexia, often compounded by overt nausea and vomiting, is a common nutritional problem. Few febrile patients are able to maintain a normal oral intake of fluids, calories, protein, and other nutrients. This problem cannot be eliminated by merely writing orders for a properly calculated dietary intake or by instructing a sick patient to eat the quantities and varieties of foods calculated to meet nutritional needs. Kindly and purposeful encouragement by family members or an attentive nursing staff may also be ineffective. Forced feeding of a severely nauseated patient is unwise. However, a sick patient should be offered soft or liquid foods of high nutrient value. When marked anorexia and nausea severely restrict food intake, some of the deficits can be minimized by using conventional intravenous fluids to maintain fluid and electrolyte balance and to supply some nutrients. Any nutritional deficit incurred during a brief self-limited or easily treated infection should be corrected by a well-managed program of convalescent-period refeeding. This aspect of nutritional support is too often ignored. On the other hand, if infections become protracted, or occur as a complication of some other severe disease process more aggressive nutritional support should be considered during the illness.

Most of the common infectious diseases can be managed by the family members at the home. Hospital based management will be required for diseases

of great severity including those that require the frequent parenteral administration of antimicrobial drugs.

The most difficult forms of infection seen in modern medical centers occur as secondary complications of other medical or surgical illnesses. Many of these infections are due to opportunistic organisms that respond poorly to available antibiotic drugs. Since infections originating in modern hospitals usually develop in patients whose nutritional status is already compromised, considerable effort may be required to reconstitute nutrient stores and build up body defensive measures.

Alimentation techniques developed to meet the unusually large nutritional requirements of severely burned or traumatized patients now allow surgeons to provide sufficient nutrients to meet high energy needs associated with hypermetabolic illnesses. This may be accomplished by infusions of nutrients into large central veins or by using a constant-drip gavage of a chemically defined diet. Gavage is accomplished through thin-walled nasogastric catheters to provide balanced free amino acid and carbohydrate mixtures. When given at proper concentrations and rates, these mixtures can be fully absorbed in the upper intestine with a minimum of digestive work; therefore, gavage can be used in patients with lower intestinal lesions. Gut mobility and nutrient absorption may be severely impaired in a nauseated patient. Thus, aggressive enteral infusion techniques carry certain risks that must be balanced against their potential benefits.

Because of the need to infuse hypertonic solutions via chronically implanted central venous catheters, total parenteral alimentation is not without danger. Microorganisms can gain access to the body through or around

the catheters and thrombus formation can occur. Hyperosmolality of the infused nutrient solutions can initiate an osmotic diuresis with dehydration and may cause impaired function of phagocytic cells. Severe hypophosphatemia can develop in patients receiving total parenteral alimentation; this reduces leukocytic ATP content and depresses the chemotactic, phagocytic, and bactericidal activities of granulocytes. Fluid overload must also be avoided. Intravenous alimentation fluids containing a high content of glucose were found to increase mortality rates appreciably in monkeys during experimental bacterial and viral illnesses associated with hepatocellular damage (7).

In individuals whose nutritional stores have been depleted by severe disease or a complex surgical problem, secondary sepsis is a relatively common complication. It is generally difficult, if not impossible, to control or eliminate the septic process in such patients by using the normally appropriate and effective antibiotic. In contrast, if supported by alimentation techniques to provide adequate nutritional intake, some patients are then able to become free of fever, clear their blood and tissues of the invading microorganisms, and heal their surgical lesions. The correction of nutritional deficiencies in such patients with severe septic complications appears to permit host defensive mechanisms to regain their functional adequacy.

Despite the potential dangers of aggressive forms of nutritional therapy, patients with severe gram-negative bacterial sepsis or long-standing infectious processes may benefit by their usage. Life-threatening septic processes due to opportunistic microorganisms can often be eliminated if appropriate antimicrobial therapy is supplemented by vigorous nutritional measures. Such demonstrations are highly instructive, for they point out

the value of nutritional therapy in an unequivocal manner. On the other hand, this form of nutritional support has not been adequately studied in life-threatening, acute hemorrhagic viral infections, and the dangers could outweigh any potential advantages.

g. Convalescent Period Therapy

Infection-induced depletions of body nutrients are reversible. However, complete restitution of nutritional losses which result from mild, self-limited infections of relatively brief duration may require several weeks, if food intake is not increased. Thus, it becomes important to provide an optimal nutrient intake during convalescence from an infection.

With the cessation of fever and anorexia, the early convalescent period represents a "nutritional window" that should be used to restore earlier losses. Some patients develop hyperphagia during early convalescence, making the replacement of nutrients an easy task if the diet is properly constituted. In nutritionally depleted children, the nutritional aim should be to obtain "catch-up" growth. Since the mother has a key role for achieving this objective, she should be instructed about the needs for providing highly nutritious foods for a period of several weeks after recovery from an infection.

The temporary presence of nutritional deficits in early convalescence predisposes a patient to secondary infections by weakening resistance mechanisms. Body nutrient stores and the functional capabilities of host defensive mechanisms are at a low point in the days immediately after fever has abated. This problem is greatest in infants and small children whose nutritional requirements for growth are superimposed on other nutritional

needs. Thus, in the growing child, an infection often creates nutritional deficits that lead to new problems with secondary infections. Such synergistic cycles are the rule rather than the exception in children who suffer from preexisting deficits of protein, calories, or both. Nutritional therapy in early convalescent may be life saving by reversing the cycle of infection, further malnutrition, and reinfection.

Because chronic malnutrition is so commonly associated with the occurrence of infectious diseases, refeeding programs should be conducted with a high degree of suspicion that a subclinical or smoldering infectious process may become activated. The nutritionist should be alert to the possible need to initiate prompt antimicrobial therapy for any such reemergent infection that occurs during a refeeding program.

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