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METABOLIC RESPONSES OF THE HOST TO INFECTIOUS DISEASE.(U)
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A review of sequential metabolic responses of the host to infectious disease. Infectious illness initiates a variety of specific and nonspecific metabolic, biochemical, endocrine, and physiological responses which are necessary in the host's defense against invading organisms. This results in alterations in protein, carbohydrate, lipid, mineral, trace element, and water metabolism of the host.

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Thyroxine
Trace metal metabolism
Triglycerides
Ureapoieses
Water metabolism

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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INTRODUCTION

An invasion by a pathogenic microorganism stimulates the body to initiate a variety of defense mechanisms. Following penetration of bacteria at a localized site, for example, the body will respond with a mobilization of phagocytes, development of a localized inflammatory response following exposure of the host. If the invading microorganisms are able to survive the initial defense reactions, the body will initiate a number of generalized host metabolic responses which, at present, do not have a well-defined defense function. These metabolic responses occur in a sequential pattern and can be documented in many infectious illnesses. The magnitude of these metabolic responses will depend upon the severity of the illness, the rate at which the specific defense mechanisms of the host are able to combat the invading microorganism, and effect of therapy. Some of the metabolic changes are analagous to the catabolic responses characteristic of trauma (Wannemacher, 1975). Other

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metabolic responses are triggered by endogenous mediators released during phagocytic activity (Pekarek et al., 1974), while many others may be characteristic of infectious disease only (Kaminski et al., 1977). The sequential metabolic changes which occur as typical manifestations of a generalized infectious process may be modified by concomitant development of unique pathogenic events such as liver cell dysfunction during viral hepatitis, muscle paralysis during poliomyelitis, progressive hypotension during gram-negative sepsis, or electrolyte depletion during cholera-like diarrhea.

INCUBATION PHASE OF THE DISEASE

Once the pathogenic microorganism has overcome the body's initial defense reactions, it will continue to proliferate to the state where the host develops infectious illness. The period of time from exposure to the onset of clinical illness is termed the incubation phase of the infection. The length of the incubation phase will depend upon the number of organisms which invade at the time of initial exposure, the replication rate of the microorganism, and pre-existing factors in the genetic, immunological, and nutritional status of the host, and even by the time of day that an infectious process is initiated (Beisel, 1975). As the organisms proliferate, local and/or systemic phagocytic cells are activated. During phagocytosis there is a burst of glucose oxidation via the pentose shunt pathway, the formation of phagocytic vacuoles, and the activation and release of many lysosomal enzymes (Klebanoff, 1971). In addition, these activated phagocytes are known to release endogenous mediators which are, in turn, capable of eliciting some of the metabolic sequelae which are associated with infection or other inflammatory reactions in the body (Beisel, 1975; Powanda, 1977). The phagocytizing cells which have been activated by the uptake of infectious organisms or

by stimulation of substances such as endotoxin, interferon inducers, phlogistic agents or products of antigen-sensitized lymphocytes will release these endogenous mediators. These mediators have been termed "endogenous pyrogens (EP)" or "leukocytic endogenous mediator (LEM)" and have been shown to travel via the blood to act on cells which are located a distance from the activated phagocyte which is responsible for their release (Atkins & Bodel, 1972; Pekarek et al., 1974). A number of investigators have shown that EP is capable of initiating a febrile response by stimulating the hypothalamus to alter the thermal regulation of the body, resulting in reduced heat loss (Wood, 1970; Atkins & Bodel, 1972). In a like manner, LEM has been shown to initiate many of the metabolic sequelae which are associated with infectious diseases (Pekarek et al., 1974). Part of the LEM effects are directed toward the liver and result in the stimulation of hepatic uptake of amino acids, zinc and iron from plasma and an increased hepatic synthesis of plasma acute-phase globulins. These effects, in combination, result in a decrease in plasma zinc and iron and an increase in plasma copper. The increased production of acute-phase globulins is associated with accelerated synthesis of bound ribosomal RNA and activation of nuclear-DNA chromatin template activity in the liver, which requires the permissive action of the glucocorticoid hormones (Thompson et al., 1976). In addition, LEM stimulates the pancreas to release both glucagon and insulin, resulting in a subsequent decrease in hepatic glycogen and an increase in adenyl cyclase activity (George et al., 1976). LEM also initiates both an increased release of granulocytes and an activation of colony-stimulating factor which mediates an increased production of granulocytes in the bone marrow (Kampschmidt & Upchurch, 1976). While it has been suggested that LEM acts directly on the target organ (Beisel,

1975), it has recently been reported (Bailey et al., 1976) that small quantities of LEM injected into the lateral ventricle of the brain in rats will stimulate depression in plasma zina and iron, uptake of amino acids by liver, and synthesis of acute-phase globulins. Further, the increased release of pancreatic hormones could influence rates of hepatic amino acid uptake and other metabolic responses associated with LEM. Thus, LEM may have a multifarious mechanism of action which results in the varied metabolic responses associated with this mediator.

Both LEM and EP have been shown to be released from a number of different cell types including granulocytes, macrophages, monocytes, and Kupffer cells (Atkins & Bodel, 1972; Beisel, 1975). Using a sensitive bioassay technique, LEM has been shown to be circulating in the plasma of patients who are febrile with many different kinds of infectious diseases (Wannemacher et al., 1975). Although LEM and EP have not been isolated in pure form, it would appear that they both contain a heat-labile, trypsin- and pronase-sensitive protein with a molecular weight of 10 - 30 000 (Beisel, 1975). The protein moieties of LEM and EP cannot be separated by methanol-butanol extraction, molecular filtration, Sephadex and ion exchange chromatography, or isoelectric focussing (Merriman, Pulliam & Kampschmidt, 1977). However, it has recently (Mapes & Sobocinski, 1977) been possible to inactivate EP by treatment with glass beads without removing various LEM activities. Further, it appears that LEM requires some prostaglandin-like synthesis for granulocytes to release biologically active material (Mapes, George & Sobocinski, 1976). Thus, it can be hypothesized that LEM and EP are similar or closely related proteins which are conjugated with various fatty acid or prostaglandin-like compounds which impart the various specific biological activities associated with these mediators.

In addition to the metabolic sequelae described above, the activity for a number of hepatic enzymes including tryptophan oxygenase, tyrosine transaminase, glycogen synthetase, and alkaline phosphatase are increased early in the infectious process (Beisel & Rapoport, 1969). The increase in these hepatic enzymes may be related to a rise in endogenous glucocorticoid secretion which takes place during this stage of the infection. Also, an increased renal loss of sodium and chloride have been detected during a brief period prior to the onset of fever (Beisel, 1975).

CLINICAL ILLNESS

As the infectious organisms continue to proliferate, the host develops characteristic syptoms of clinical illness, which include fever, malaise, myalgia, and anorexia. In addition, unique pathogenic effects will be noted in organs which are specifically susceptible to a particular organism, such as respiratory tract during pneumonia or influenza, vomiting and diarrhea associated with enteric organisms, or the rashes associated with measles or scarlet fever. The most predominant metabolic response during the febrile infection is the wasting of body tissues (Beisel, 1975). Since widespread catabolism of body tissues does not begin until after fever has become fully evident, fever would appear to be the major stimulus for initiating catabolic losses during an infectious illness.

With the onset of clinical illness the basal metabolic rate can be elevated 20 - 50 per cent above that observed in normal resting man (Du Bois, 1948). Du Bois (1948) called attention to the remarkable parallelism in infectious fever between the body temperature and the height of total metabolism. This led to the conclusion that higher body temperatures would speed the velocity of chemical reactions and could result in an increase in metabolic rate. Therefore, fever during

infectious illness is the result of alterations both in the thermal regulatory mechanism resulting in decreased heat loss, probably under the regulation of endogenous pyrogen, and a concomitant increase in heat production which is associated with the elevated metabolic rate.

The fractional disappearance rates of both thyroxine and triiodothyronine from plasma are increased during acute infectious illness, with resulting depression in protein-bound iodine (Beisel, 1975). This alteration in the metabolism of thyroid hormones may be related to increases in metabolic rate.

1. PROTEIN CATABOLIC RESPONSE

As illuatrated in Table 1 various infectious diseases will result in a marked increase in the rate of excretion of urinary nitrogen. In other infections increased amounts of nitrogen can also be lost through the stool and sweat (Beisel, 1975). The losses in body nitrogen are related to the wasting of body tissues and are proportional to the loss in quantities of other intracellular elements such as K, P, Mg, S, and Zn. The increased excretory loss of nitrogen coupled with reduced dietary intake results in marked negative balances during infectious illness. In contrast, if the protein intake of a normal person is lowered or discontinued, the body responds by quickly reducing urinary nitrogen losses (Table 1). Further, during experimentally induced tularemia in volunteers an average cumulative loss of almost 60 gm of body nitrogen occurred despite prompt treatment (Beisel et al., 1967). If normal volunteers were pair-fed the same dietary protein and calorie intake as that consumed during the tularemia infection, they lost only 15 gm of body nitrogen. Therefore, the anorexia is not the stimulus for the increased wasting of body protein, associated with febrile infection.

The adrenocorticoids are secreted in increased amounts during stress

and have long been considered the catabolic hormones (Beisel & Rapoport, 1969). Since they seem likely candidates as regulators of much of the metabolic changes during infection, glucocorticoid response was studied during several infections. Bacterial (tularemia), mild viral (sandfly fever), and rickettsial infections (Q fever) were employed in these studies. All of these infections stimulated an almost two-fold increase in the amount of 24-hr urinary 17-hydroxycorticosteroid excretion during the febrile phase of the infection. The morning febrile samples showed little difference in the plasma total or free 17-hydroxycorticosteroids; however, in healthy subjects the plasma concentrations showed a normal circadian rhythm with a decrease in concentration in the afternoon or evening. In contrast, there was no decrease in either total or free plasma 17-hydroxycorticosteroids in the febrile samples of volunteers with any of the infections studied. Thus, the apparent loss of steroid periodicity in plasma could account for the increase in urinary excretion of glucocorticoids. The question was then raised as to whether the modest increase in production of adrenal glucocorticoids during the febrile phase of the infection could account for the marked catabolic response. When healthy subjects were given oral doses of glucocorticoids to increase the urinary 17-hydroxycorticosteroids to the concentration seen during the febrile phase of the infection, no increase in the excretion of urinary nitrogen occurred (Table 1). Therefore, it was concluded that the glucocorticoids themselves were not solely responsible for the marked catabolic changes observed during febrile infectious illness.

The severity and duration of fever during acute infection appears to be correlated with the magnitude of the catabolic losses (Du Bois, 1948); Beisel et al., 1967). However, should an infectious process become subacute or chronic as is seen typically in patients with advanced

tuberculosis or repeated febrile episodes of malaria, daily losses of nitrogen and intracellular elements become progressively less and eventually the patient enters the chronic state of cachexia and protein depletion (Howard, Bigham & Mason, 1946). Despite the inability of fever to elicit increased nitrogen loss in the malnourished patient, it did increase the basal metabolic rate to that which is customarily observed during an increase in body temperature.

To measure the effects of physically induced fever on metabolic balances in man, healthy well- nourished volunteers were exposed to elevated environmental temperatures to produce hyperthermia similar to that observed during the febrile phase of bacterial infections (Beisel, Goldman & Joy, 1968). The induced hyperthermia resulted in an increased urinary loss of nitrogen and potassium, persisting for one day after body temperature had returned to normal (Table 1). Thus, elevated body temperatures associated with febrile infectious disease appear to be the stimulus for increased wasting of body proteins, which may be the result of the temperature-induced increase in many biochemical reactions of the body. This relationship, however, on protein metabolism was not observed in the malnourished patient.

The major nitrogenous component which is increased in urine during febrile infection is urea nitrogen (Beisel et al., 1967). This increase in ureapoiesis is the result of accelerated rates of catabolism of amino acids derived from body proteins. Since skeletal muscle contains approximately 40 per cent total body proteins (Wannemacher, 1975), muscle has been suggested as the major source of protein for the accelerated rates of catabolism during the febrile phase of an infectious process. A number of studies in experimental animals have demonstrated that protein synthesis is markedly reduced in muscle very early in infectious disease (Wannemacher,

1975). In addition, several points of evidence suggest that the degradation of skeletal muscle protein is accelerated during the febrile period of infection. These include an increase in the rate of urinary excretion of 3-methylhistidine, creatine, and creatinine (Beisel, 1975; Wannemacher, 1975). In addition, when the muscle of rats was prelabeled with [^{14}C]phenylalanine and the rats were subsequently infected, they expired more labeled CO_2 than did those injected with heat-killed organisms, which is consistent with the concept of an increased rate of protein catabolism during infectious disease (Wannemacher & Dinterman, 1977). Thus, a combined decreased rate of synthesis and an increase in rate of degradation of skeletal muscle proteins would result in an elevated supply of endogenous amino acids and could account for the catabolic response associated with infectious disease.

Because of the reported increased utilization of amino acids, studies were initiated to determine what effect infection would have on the free amino acid pools of plasma. Regardless of their etiology, all of the infectious diseases studied resulted in significant depression of total plasma amino acids (Wannemacher, 1977). During infections in man the pattern of change of individual plasma free amino acids was markedly different from that observed in simple starvation and no difference was observed in the rate of excretion of total urinary amino acids. Thus, the changes in plasma amino acids do not represent alterations in renal clearance or reabsorption, nor are they the result of infection-induced anorexia. This led to the suggestion that the observed change in plasma amino acids was the result of the redistribution and utilization in various tissues of the body. By use of labeled nonmetabolizable amino acids, it was possible to demonstrate a marked flux of amino acids into liver from skeletal muscle. Many individual plasma amino acid

concentrations are depressed during infectious illness, with the largest decrease observed in the branched-chain amino acids. In contrast, plasma phenylalanine and tryptophan concentrations are increased in both bacterial and viral infections. This increase is correlated with an accelerated rate of release of these amino acids from skeletal muscle, resulting in elevation in the phenylalanine:tyrosine ratio and excretion in urine of excess tryptophan metabolites produced via the kynurenine pathway (Wannemacher, 1977).

One of the major hepatic utilizations of amino acids is via the gluconeogenic pathway. In this pathway, the amino acids are deaminated and the carbon skeleton is utilized to synthesize glucose, while the amino nitrogen is converted to urea. Thus, an accelerated rate of gluconeogenesis could explain the elevated nitrogen loss seen during a febrile reaction. The major gluconeogenic substrates for the liver are alanine and lactate (Felig, 1973). A review of the literature indicates that alanine is one of the major amino acids released from skeletal muscle and its concentration is far greater than is possible based upon the molar ratio of alanine in the proteins of skeletal muscle (Felig, 1973; Wannemacher, 1977). This paradox has led to the suggestion that the amino group and perhaps the carbon skeleton of amino acids which are catabolized in skeletal muscle are converted to alanine for subsequent transport to liver to be utilized in the gluconeogenic pathways. It has recently been reported (O'Donnell et al., 1976) that in septic patients the rate of release of alanine from skeletal muscle was increased four- to five-fold over that observed in fasting subjects and the arterial concentration of these substrates was elevated two- to three-fold. This accelerated release of gluconeogenic substrates from skeletal muscle and hepatic uptake could lead to elevated rates of gluconeogenesis during fe-

brile illness. An increased gluconeogenic rate from labeled alanine has been observed in septic patients and could not be inhibited by infusion of a 5 per cent dextrose solution (Long, Kinney & Geiger, 1976). This suggests that the accelerated rates of gluconeogenesis during febrile infection are regulated by the increased availability of gluconeogenic substrates. In contrast, in cachectic patients or infants, muscle protein pools are very small and gluconeogenic substrates cannot be produced at an elevated rate, which prevents the increased loss of nitrogen observed during infection in well-nourished individuals.

2. PROTEIN ANABOLIC RESPONSE

While infectious illness is characterized by marked wasting of body proteins, many anabolic responses are brought into focus. These may be antibodies which are specific for the causative microorganisms or they may be nonspecific responses which are characteristic of infectious disease. All these anabolic responses require the availability of added quantitities of cellular energy as well as intact protein synthesizing mechanisms within the stimulated cells (Beisel, 1975). The specific response requires the presence of cells which the causative microorganism stimulates to release factors which cause B-lymphocytes to synthesize specific immunoglobulins and T-lymphocytes to release the lymphokines which are characteristic of cell-mediated immunity (Beisel, 1975); Wannemacher, 1975). The process also stimulates the production of components of the complement system and interferon. Simultaneously, this process stimulates increased phagocytic activity in the granulocytes and macrophages. During phagocytosis there is a burst of metabolic energy within the cell, formation of phagocytic vacuoles, and activation and release of many lysosomal enzymes and mediators.

As noted earlier, one of these mediators stimulates hepatic

production of acute-phase proteins including α_1-antitrypsin, α_1-acid glycoprotein, haptoglobulin, fibrinogen, C-reactive protein, ceruloplasmin, and C-3 complement (Pekarek et al., 1974; Bostian et al., 1976). The rate of synthesis and accumulation of acute-phase proteins in plasma will depend upon the severity of the illness and the causative microorganisms (Bostian et al., 1976; Wannemacher & Beisel, 1976). Although the function of these acute-phase proteins has not been elucidated as to their contribution to the host defense mechanism, some evidence is accumulating which suggests that they may play a role in minimizing the tissue damage associated with phagocytes and amplifying the humoral and cell-mediated responses of the host (Powanda, 1977). Since the synthesis of these acute-phase globulins is increased even during periods of starvation or extreme protein-calorie malnutrition (Beisel, 1975), they would appear to have a high priority for utilization of the endogenous amino acid supply during infectious illness. Thus, in the malnourished patient or in the infant, where muscle protein stores are small and a supply of endogenous amino acids is decreased, marked competition exists for the utilization of these amino acids between the liver for synthesis of acute-phase proteins and gluconeogenesis, the cells involved in specific host defense against the causative microorganism, and the protein synthesis necessary for the normal homeostasis of the host. This competition results in a magnification of the depletion of the host and an inhibition of some of the specific host defense mechanisms (Wannemacher & Beisel, 1976).

3. ALTERATIONS IN CARBOHYDRATE METABOLISM

During the early febrile phase of many infectious illnesses, fasting plasma concentrations of glucose are significantly increased above those seen in normal fasted subjects (Beisel, 1975; O'Donnell et

al., 1976), Despite the tendency towards increased hyperglycemia, Long et al: (1971) observed a doubling of glucose-pool size which is associated with an increased rate of glucose turnover and oxidation in septic patients. Recent studies in animal models indicate that the increased rate of oxidation of glucose is related to elevated activity in the pentose shunt pathway (Wannemacher, 1977). Since this pathway is the major source of energy in the actively phagocytizing cell, the increase in glucose oxidation during febrile illness may be related to elevated rates of phagocytosis of the causative microorganism.

In addition to the hyperglycemia, fasting plasma concentrations of insulin, glucagon, and growth hormone are increased during a febrile infection (Beisel, 1975). The insulin:glucagon ratio is decreased which favors activation of adenyl cyclase, formation of cyclic AMP and resetting of hepatic glycogen synthetase and phosphorylase enzymes to favor glycogenolysis (Beisel, 1975). If during illness, carbohydrate tolerance is measured by means of intravenous glucose load, the disappearance rate for both glucose and insulin is significantly decreased and approaches those characteristics of borderline diabetes. The reduced ability to dispose of the glucose load in the febrile infections could be related to the decreased ability to synthesize glycogen. Thus, during infectious illness the body is geared for an increased production of glucose as an energy source and a reduced potential for storage of this metabolic fuel.

4. ALTERATIONS IN LIPID METABOLISM

During fasting and starvation in normal subjects the body will adapt by increasing ketone production from fatty acids which are utilized in place of glucose as a metabolic fuel in tissues such as brain and skeletal muscle (Cahill, Owen & Morgan, 1967). This results in a conservation of body protein and a mobilization of the fat depots. During febrile

illness in man and experimental animals, however, the development of starvation ketosis is inhibited and the ketones are not available as metabolic fuels for skeletal muscle (Neufeld, Pace & White, 1976; O'Donnell et al., 1976). The skeletal muscle of septic patients has an impaired rate of glucose oxidation, free fatty acid uptake, and lipolysis as well as ketone availability (O'Donnell et al., 1976). Since muscle accounts for 30 - 40 per cent of total oxygen consumption in fasted man and this is increased to 10 - 30 per cent in sepsis, this tissue must utilize an alternative fuel to meet the reduced energy supply from glucose and fat. The oxidation of the branched-chain amino acids could satisfy this requirement. Correlation exists between the rate of oxidation of the branched-chain amino acids and loss of muscle proteins (O'Donnell et al., 1976; Wannemacher, 1977). The increased availability of amino groups from the oxidation of the branched-chain amino acids and availability of pyruvate from impaired glucose oxidation will result in increased alanine production during infectious illness. The increased rate of peripheral oxidation of the branched-chain amino acids would also explain the marked decrease in plasma concentrations of these amino acids which has been observed in a number of infectious illnesses (Wannemacher, 1977). Further, the elevated production of alanine and lactate stimulate the liver to increased rates of gluconeogenesis and ureapoiesis characteristic of body wasting.

In general, plasma triglyceride concentrations are increased during the febrile phase of many infections, being most marked during gram-negative bacterial sepsis (Beisel, 1975). When labeled fatty acids were given during febrile illness, they disappeared from the plasma more rapidly and the rate of triglyceride and cholesterol synthesis within the liver was accelerated. Both histological and biochemical analysis suggest

increased accumulation of triglycerides in the liver of infected animals. It is hypothesized that the liver of the infected host shunts the fatty acids away from beta oxidation and ketone production and toward the synthesis of triglycerides. In addition, the infectious process is associated with reduced disposal of triglycerides because of a progressive decrease in post-heparin lipolytic activity (Kaufmann et al., 1976). Thus, the increased hepatic synthesis and decreased disposal of triglycerides in the infected host results in accumulation of these moieties in the plasma.

Changes in plasma free fatty acid concentrations are quite variable depending upon the severity and etiology of the infectious disease (Beisel, 1975). However, when compared sequentially to fasted controls, the plasma free fatty acids are decreased during most infectious diseases (Neufeld et al., 1976). A reduction in food intake results in an increase in lipolysis of adipose fat stores and a resultant elevation in plasma free fatty acid concentrations. This increase in plasma free fatty acids is prevented in the infected host, which may be related to reduced mobilization of adipose lipids, as a consequence of the hyperinsulinemia associated with an infectious process (Neufeld et al., 1976). It is also possible that the decreased concentration of free fatty acids represents an increased utilization by peripheral tissue. However, O'Donnell et al. (1976) observed a decreased utilization of free fatty acids by skeletal muscle of septic patients.

5. ALTERATIONS IN SALT AND WATER METABOLISM

With the onset of fever, aldosterone secretion is increased resulting in an avid retention of Na and Cl by the kidneys (Beisel, 1975). During periods of high fever both Na and Cl may disappear from the urine. At the same time, the secretion of antidiuretic hormone may become

inappropriate, leading to retention of water by the kidneys and accumulation of extracellular water during fever.

6. CHANGES IN MINERAL AND TRACE METAL METABOLISM

Slight declines in the plasma concentrations of Ca and Mg are noted during the febrile period of infection and may be the result of dilutional effects of increased extracellular water (Beisel, 1975). The plasma concentration of Fe and to a lesser extent Zn are markedly diminished during acute infectious illnesses (Wannemacher et al., 1976). Although both transferrin and albumin are slightly decreased during the latter stages of infectious disease, the depression in these carrier-proteins for Fe and Zn is not responsible for the marked reduction in the plasma concentrations of these trace elements. Rather, the decreases in plasma Fe and Zn represent a redistribution and accumulation in liver which is stimulated by mediators released from phagocytic cells. In severe pyrogenic bacterial infections, Fe may virtually disappear from the plasma, leading to anemia if the infection becomes chronic.

During severe infections, especially gram-negative bacterial sepsis, the plasma concentrations of inorganic phosphorus (Pi) can be decreased. This hypophosphatemia may occur in part as a manifestation of respiratory alkalosis due to the hyperventilation typically associated with rising body temperature (Beisel, 1975). Also, the plasma concentration of Cr is reduced during infectious illness (Pekarek et al., 1975). This decrease in Cr is correlated with reduced glucose disappearance rates in infected subjects.

Unlike the decline in Fe, Zn, Cr, and Pi, plasma Cu concentrations are increased in most bacterial and viral infections (Wannemacher et al., 1976). This increase in the concentration of plasma copper can be ascribed to the elevated production of ceruloplasmin (the major protein-

carrier of Cu) by liver and its accumulation in plasma.

TERMINAL ILLNESS

If an individual develops an overwhelming severe infection, body temperature will decrease resulting in the development of hypothermia during the final phases of the illness. Associated with this hypothermia is hypoglycemia, especially during endotoxemia in newborns with sepsis, or in patients with severe liver damage, such as may occur with yellow fever or viral hepatitis (Beisel, 1975). In addition, these patients develop marked hypoketosis and hypertriglyceridemia. Thus, in terminal illness, patients are unable to synthesize glucose at the rate necessary to meet the energy requirements which, in combination with inability to utilize fatty acids or synthesize ketones, results in a marked depletion of available energy substrates. This leads to decreased rates of oxidation and heat production, as well as starvation of cells necessary for maintenance of homeostasis within the host.

CONVALESCENCE

With lysis of fever and other clinical signs of illness, the convalescent phase of the infectious disease begins. In the well-fed patient nitrogen is retained and repletion of body stores begins. On a protein intake which maintains nitrogen equilibrium in the healthy volunteer, it took 1 to 2 days after lysis of fever to reach nitrogen equilibrium in those volunteers who were ill with various infectious diseases (Beisel et al., 1967). During a mild viral illness in which volunteers lost 20 gm of nitrogen over a 4-day period, nearly 15 days were required to recover all of the nitrogen which had been lost during the illness. In a much more serious bacterial illness in which the volunteers lost 60 gm over 6 days, less than 50 per cent of this nitrogen was replaced when they were fed a maintenance diet for 15 days after lysis of fever. Similar slow rates of

repletion were also noted for the loss in body potassium and magnesium. Thus, these data confirm the earlier observations of Du Bois (1948) and emphasize the observations that a generalized infectious process does cause a loss in body nitrogen beyond that associated with anorexia, and that during convalescence it takes a relatively long time to replenish this loss in body nitrogen. A subsequent recurrence or new infection during this period of convalescence will result in further depletion of body proteins which will eventually result in protein-calorie malnutrition.

The basal metabolic rate can remain elevated (10 - 15 per cent above normal) for 4 to 5 weeks following lysis of fever in typhoid fever patients (Du Bois, 1948). During convalescence the increase in basal metabolism cannot be related to the temperature-induced elevation in the velocity of chemical reactions. This increase in metabolic rate may be due to the enhanced secretion of thyroxine and increase in protein-bound iodine which have been observed during convalescence from infectious diseases (Beisel, 1975).

Both Na and Cl are retained by the kidney for a day or two after lysis of fever. This is associated with diuresis occurring in the postfebrile period of convalescence, resulting in a slight increase in plasma concentrations of Na and Cl (Beisel, 1975). With lysis of fever plasma concentrations of Fe and Zn gradually increase and the urinary excretion of Zn and Cu is elevated (Beisel, Pekarek & Wannemacher, 1974).

The plasma concentration of a number of the acute-phase globulins are elevated above normal for as long as a week after lysis of fever in volunteers ill with typhoid fever (Bostian et al., 1976). Since the half-life of many of these proteins is 1 - 2 days (Powanda, 1977), the synthesis of the acute-phase globulins is continued at an elevated rate

for a number of days after the cessation of febrile illness. In contrast, plasma albumin and transferrin remained depressed during the 1-week convalescent period that the volunteers were observed. The depression in these two plasma proteins is a good clinical indicator of the protein-depleted state of the host during the week after lysis of clinical illness.

The concentration of nonspecific IgM continues to increase during the convalescent period in the infectious illness (Bostian et al., 1976). During this time period the synthesis of specific IgM against the infectious microorganisms will decrease, while the synthesis of specific IgG will be stimulated and elevated concentrations of these specific antibodies can be observed a month or more after cessation of clinical illness.

Thus, alterations in host metabolic processes, including protein depletion, continue for an extended period of time after cessation of clinical illness. During this time period when a patient is recovering from an infectious illness, he would be most susceptible to a secondary or superimposed microbiological invader. Thus, prompt and expeditious measures to correct the nutritional depletion associated with infectious disease should be the important goal in the management of convalescent patients. Unfortunately, patients and physicians alike generally assume that a complete cure has been achieved when the fever and symptoms of acute illness disappear, while in reality this may be the most important time period, nutritionally, to overcome the depletion associated with the infectious disease and to stimulate the host defense mechanisms against future invading organisms.

SUMMARY

Infectious illness initiates a variety of specific and nonspecific metabolic, biochemical, endocrine, and physiological responses which are necessary in the host's defense against the invading organisms. Many of the nonspecific responses are characteristic of most infectious diseases and are associated with the mobilization of body protein for the synthesis of those proteins necessary for the host's defense against the infectious organism and for the production of glucose to be oxidated as a source of energy. The infection process results in a decreased ability to utilize the fat stores of the body and an increased dependency upon carbohydrate and protein stores. In addition, there are alterations in the mineral trace element and water metabolism of the host. The depletion of body nutrients continues well into the early phases of convalescence, resulting in a lengthy period of time required to replace these losses. Nutritional support can be used to minimize the losses during infectious illness and can be employed effectively to replace the lost nutrients as expeditiously as possible during convalescence.

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TABLE 1. Urinary nitrogen excretion in normal and fasted subjects during febrile infection and hyperthermia

Treatment	Urinary N gm/day	Reference
Normal*	13	Beisel et al., 1967
Normal + cortisol (25 - 30 mg/day)	13	Beisel et al., 1967
Fasted -- 72 hr	7 - 11	O'Donnell et al., 1976
28 days	4	Owen et al., 1967
Typhoid fever	18 - 25	Shaffer & Coleman, 1909
Pneumonia	20 - 25	Grossman et al., 1945
Scarlet fever	18 - 20	Grossman et al., 1945
Meningitis	20 - 30	Grossman et al., 1945
Malaria	20	Howard et al., 1946
Tularemia	16 - 17	Beisel et al., 1967
Sandfly fever	15 - 16	Beisel et al., 1967
Q fever	16 - 18	Beisel et al., 1967
Sepsis	16 - 22	O'Donnell et al, 1976
Hyperthermia -- 1 day	15	Beisel et al., 1968
following day	20	Beisel et al., 1968

* Intake 14 - 15 gm N and 2 500 - 2 800 cal/day.