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Alterations in hormone production and utilization during infection

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I. GENERAL CONCEPTS

The defensive responses of a human or animal host against infectious microorganisms are broad and complex, involving a large variety of physiological, biochemical, metabolic and hormonal activities. As host-initiated components in the pathogenic progression of an infectious disease, these responses develop and then disappear in a coordinated, relatively orderly sequential manner. Such responses typify quickly resolved acute infections and follow a stereotyped pattern despite the many different kinds of microorganisms that may cause such an illness. On the other hand, should an infection progress instead of subsiding, additional, more unique responses may emerge in conjunction with the development of chronicity, complications or terminal events (Beisel, 1977).

A central position in this broad array of host responses is filled by certain endocrine glands and their hormones. The endocrine aspects of the host response to infection are also complex, but coordinated. They include an important involvement of the anterior and posterior pituitary glands, the adrenal cortex, thyroid, endocrine pancreas, and sometimes the adrenal medulla. In contrast, neither parathyroid glands nor gonads have an immediate or recognized participatory role in dynamic hormonal responses during acute infectious illness.

More than three decades ago, Selye (1946) stimulated the field of endocrinology with his concepts of stress and the general adaptation syndrome. The adrenal cortex was singled out as the primary responding endocrine gland during stress and Selye postulated an initial period of adrenocortical hyperfunction, the so-called 'alarm reaction.' If stress persisted, the initial phase of adrenal activation was believed to be followed by a state of adrenal exhaustion. Hormonal data obtained during infectious illnesses support some aspects of the Selye concept, i.e., the short-lived initial increase in glucocorticoid secretion at the onset of fever and the prolonged period of diminished adrenocorticoid hormone production during chronic or protracted infections. However, the brief increase in adrenocortical hormone output is insufficient to account for the catabolic aspects of acute infection (Beisel and Rapoport, 1969a, b). In fact, normal volunteers given cortisol in a sequence of doses to mimic the actual

pattern of glucocorticoid output measured during acute tularemia failed to exhibit any loss of body nitrogen in balance studies (Beisel et al., 1967b). Further, the magnitude and extent of other endocrine responses during infection make Selye's concept of an alarm reaction far too narrow and too simplistic to be of current value. Rather, the hormonal responses to infectious stress are now known to involve a multiendocrine participation during acute generalized infectious illnesses. Relatively predictable, transient patterns of hormonal response emerge longitudinally depending on whether the infections terminate uneventfully, proceed to a lethal outcome, or settle into a subacute or chronic illness.

To define the stereotypic endocrine response patterns during infection, it is first necessary to measure the sequential changes in secretion and metabolic degradation of individual hormones during brief, uncomplicated illnesses. Only then can the additional influences of disease severity be evaluated, and the effects of secondary endocrine responses be delineated during complications or progressive stages of illness. Insights can be gained by the study of animal models, but many important data can be obtained only by clinical research performed in patients with naturally acquired or experimentally induced infections. Such data are still quite limited, in large part because endocrine study technologies have always required advanced levels of laboratory sophistication and high costs.

II. ADRENOCORTICOID RESPONSES TO INFECTION

Evidence for an important adrenocortical participation in host defenses against infectious illnesses came initially from the direct study of adrenal gland pathology. In overwhelming infections, adrenal weight is generally increased and cells throughout the cortical areas appear hypertrophic. The likelihood of increased functional activity is reinforced by an accompanying depletion of adrenocortical cholesterol, total lipids and ascorbic acid (Beisel and Rapoport, 1969a, b).

On the other hand, infectious illnesses can lead to acute or chronic adrenocortical insufficiency. Acute adrenal failure results from pathogenic processes which cause bilateral hemorrhagic necrosis or destruction of the glands. This complication can be a manifestation of disseminated intravascular coagulopathy during certain bacterial (meningococcemia), viral (hemorrhagic fevers), or rickettsial (Rocky Mountain spotted fever) infections.

Chronic adrenal failure can develop as a consequence of direct glandular destruction by invading microorganisms. Adrenal localization is not uncommon during miliary tuberculosis or disseminated chronic fungal diseases. Such chronic destructive processes are often accompanied by adrenal calcification which is easy to detect roentgenographically. Chronic forms of adrenocortical destruction must be differentiated for purposes of replacement hormonal therapy from the diminished secretion of adrenocortical hormones which

characterize virtually all symptomatic subacute and chronic infectious illnesses.

A. *Glucocorticoid hormones*

An increased adrenocortical secretion of cortisol typically begins with, or somewhat before, the onset of the febrile stage of an infection. As compared to cortisol responses during physical trauma or surgery, the infection-induced increase is relatively small in magnitude. Further, the period of increased cortisol secretion is relatively brief, and elevated steroid values characteristically revert to normal even before the cessation of fever, and sometimes as soon as the clinical course of illness begins to improve. If infections become subacute or chronic, cortisol secretion is reduced and tests of adrenal function using ACTH or metyrapone may show subnormal results.

1. *Urinary glucocorticoid values*

A variety of urinary measurements, progressing through the years as technology improved from cortin, to total urinary corticoids, to 17-hydroxycorticosterone (17-OHCS) and finally to cortisol and its metabolites, tetrahydrocortisol and tetrahydrocortisone, have documented infection-induced increases in glucocorticoid excretion. Modest increases occur in diverse infections such as early pneumonia and bacterial meningitis (Bassøe, 1969), childhood virus infections, early hepatitis, acute tuberculosis, common respiratory infections, and experimentally induced tularemia, sandfly fever and Q fever (Beisel et al., 1967a, b). While urinary measurements of various 17-OHCS metabolic products of cortisol have considerable value, specific assays for cortisol itself reflect most directly the magnitude and duration of cortisol increases in plasma during early infection (Rayfield et al., 1973).

In a unique prospective study, Mason et al. (1979) measured daily urinary 17-OHCS excretion throughout the basic training period in a group of military recruits. Some of these physically stressed men developed a severe respiratory adenovirus illness during the study. Sporadic elevations of urinary 17-OHCS values were noted in individual recruits during the 2—4-day period before their illness; a more consistent tendency for 17-OHCS excretion to increase occurred the day before fever began, and increases to about 60% above baseline values were then seen during the next several days of illness.

An abrupt decline from increased to normal 17-OHCS values during the continued presence of fever has been noted in coincidence with the onset of clinical recovery by Beisel et al. (1967a, b) and Bassøe (1969). A similar phenomenon was associated by Lorenz and Rossipal (1965) with the appearance of the rash in childhood measles. A hypothalamic-pituitary-mediated mechanism accounting for the abrupt termination of cortisol excess has not, as yet, been identified.

A diminished 17-OHCS output in urine has been observed consistently in chronic tuberculosis, hepatitis and leprosy. Similar low values have been found

during the more protracted stages of poliomyelitis, psittacosis, brucellosis, malaria, or chronic dermatitis (Gemzell, 1956; Beisel and Rapoport, 1969a, b)

2. Plasma glucocorticoid values

Cortisol or 17-OHCS values in plasma increase to varying degrees during the acute stages of infectious disease. In comparison to measurements in control subjects, infection-induced changes are related to disease severity, as well as to the time of day a sample is obtained. Slight increases have been detected in children who received smallpox or attenuated measles vaccines (Hassan et al., 1972). A further increase in plasma values can generally, but not always, be achieved in the presence of an acute illness by adrenocortical stimulation achieved with ACTH or metyrapone administration (Frenkel et al., 1964; Gilliland et al., 1968; Takakura et al., 1972; Zeitoun et al., 1973). Wajchenberg et al. (1978) reported that patients with *Neisseria meningitis* or typhoid fever had consistently increased plasma cortisol concentrations, but these values increased still further in response to β^{1-24} -corticotropin stimulation unless petechiae were present. Although this observation was not interpreted as an indication of adrenal insufficiency, plasma 17-OHCS concentrations are known to fall abruptly to undetectable values if adrenal apoplexy supervenes during an acute infection (Migeon et al., 1967).

Increases in 17-OHCS values observed in plasma during acute infection must be considered as an algebraic summation of the combined effects of cortisol secretion and removal rates. Both the increased rates of cortisol production by the adrenal cortex and the factors that influence cortisol degradation within the liver to water-soluble metabolites must be considered.

The earliest change in 17-OHCS values during acute infection is a loss of the normal diurnal decline throughout the afternoon-evening hours. In mild infections, 17-OHCS values do not exceed the normally high morning-hour concentrations. Rather, they tend to remain near the upper-normal morning values, but without a diurnal fall (Beisel and Rapoport, 1969; Gilliland et al., 1968). Values somewhat above the normal morning-hour range develop in infections of greater severity in man and experimental animals (Migeon et al., 1967; Beisel and Rapoport, 1969a, b; George et al., 1974).

In patients with very severe acute infections, 17-OHCS values consistently exceed the upper limits of normal, increasing by as much as 200%. Values in this high range are explained, in part, by some degree of hepatic dysfunction, as illustrated by patients with falciparum malaria whose high plasma 17-OHCS values for water-insoluble steroids contrasted with concomitantly low urinary 17-OHCS excretion rates (Gilliland et al., 1968; Brooks et al., 1969). Melby and Spink (1958) found high plasma 17-OHCS values during bacterial shock; hormone clearance rates from plasma were accelerated in patients who survived, but were markedly slowed in patients who died. Sandberg et al. (1956), Migeon et al. (1967) and Murray (1967) have all ascribed the extraordinarily high plasma 17-OHCS values of dying patients to impaired hepatic capabilities

for degrading cortisol to its water-soluble metabolites.

There is no evidence to suggest that the normal affinities for cortisol of the cortisol-binding proteins in plasma, i.e., cortisol-binding globulin and albumin, are altered in the presence of infection (Beisel et al., 1967a, b; Murray, 1967). These plasma proteins help to regulate the concentrations of free, unbound cortisol available for interaction with cells or for passage across the blood-brain barrier. Spinal fluid steroid values thus reflect the changes observed in plasma during septic meningitis and other infections (Murphy et al., 1967; Uete et al., 1970).

3. *Cortisol production rates*

Estimations of daily cortisol production have been accomplished in man using isotope dilution techniques. Cortisol production rate measurements normally require a 48-h period of steady-state conditions. Although an acute infectious illness does not achieve steady-state conditions, the reported magnitudes of increased cortisol production (Bassøe et al., 1965; Preeyasombat et al., 1965; Ichikawa, 1966; Migeon et al., 1967) during infection are in keeping with indirect estimates based upon urinary 17-OHCS excretion values. During acute infections such as erysipelas, measles, chicken pox, bacterial pneumonia and various forms of acute meningitis, measured increases in cortisol production ranged from 1.5- to 6.0-times normal. In contrast, increases were not always seen during the subacute stages of typhoid fever or bacterial endocarditis.

B. *Adrenal androgens*

Measurements of urinary 17-ketosteroids (17-KS) and ketogenic steroids during infectious illnesses consistently reflect the direction of change observed with 17-OHCS. However, the 17-KS increases seen with acute illness are smaller in magnitude than those of 17-OHCS. Low 17-KS output is typical during chronic infections, and responses to ACTH, based on urinary 17-KS excretion, are also poor during a chronic phase of illness.

The urinary excretion of specific androgens has been measured in only a single study (Beisel et al., 1967a); slight increases in dehydroepiandrosterone and pregnanetriol occurred coincident with those of 17-OHCS and 17-KS during acute early tularemia, but no changes were detected in androsterone or etiocholanolone output. Although etiocholanolone is known to be pyrogenic if injected i.m. in man, this steroid does not appear to participate in the initiation or maintenance of infection-induced fever.

C. *Aldosterone excretion*

Acute febrile illness in man is accompanied by the renal retention of sodium

and chloride, and convalescence is typically accompanied by a diuresis of any retained salt. In keeping with these renal responses, an increase in urinary aldosterone excretion was found to begin with the onset of fever in acute tularemia and to persist until fever had subsided (Beisel et al., 1967a). Thus, the increases in aldosterone excretion did not coincide entirely with increases of 17-OHCS which tended to begin earlier during infection and then to return abruptly to baseline values as illness began to improve. Increased aldosterone excretion also coincided with renal salt retention in malaria (Brooks et al., 1967) and was detected during endotoxin shock in dogs (Spink, 1962; White et al., 1967).

D. *Responses to pyrogens*

Injection of a sublethal dose of killed gram-negative bacteria or purified bacterial lipopolysaccharide (LPS) is followed within several hours by the onset of fever in man (and some animal species) and by the release of anterior pituitary hormones and adrenal steroids. In normal subjects, the magnitude of increased 17-OHCS excretion in urine reflected the administered dose of LPS (Janches et al., 1965). In contrast, an injected dose of etiocholanolone which produced fever of equal intensity failed to trigger such a pituitary response (Kimball et al., 1968). Because of its ability to stimulate the anterior pituitary, LPS injections have been used in man as a test of pituitary function, with growth hormone, ACTH, TSH, or various plasma or urinary steroids (cortisol, 17-OHCS, 17-KS) being measured to determine the magnitude and extent of glandular stimulation. These responses have also been used in animal models to study a variety of physiological responses including the induction of hypotensive shock (Wexler et al., 1957).

In terms of an LPS-induced increase in steroidal production, pituitary responsiveness in man has a diurnal periodicity (Takebe et al., 1966). Responsiveness, as measured by increased steroidal output in urine, was maximal if LPS was given at 11:00 p.m., but was virtually nondetectable if the same dose of LPS was given at 9:00 a.m., a time when normal plasma cortisol concentrations are typically near their highest point each day.

In laboratory animals, endotoxin tolerance develops for the adrenal glucocorticoid response as it does for fever production (Bassøe, 1969). Melby et al. (1969) used varying doses of endotoxin in dogs to study the rates of 17-OHCS clearance from plasma; clearance rates were normal in dogs receiving a pyrogenic dose of LPS but were markedly slowed when lethal doses were given. Since endotoxin is hepatotoxic at high doses, this observation helped to confirm that impaired hepatic function, with a diminished ability of the liver to hydroxylate cortisol to water-soluble compounds, was a contributory mechanism responsible for unusually high plasma 17-OHCS concentrations in dying patients.

III. ADRENOMEDULLARY RESPONSES

A. *Studies in animals*

The most extensive studies of catecholamine response have been done during experimental endotoxin shock in dogs. Although responses varied with the dose of LPS administered, the analytical methods used, and the biological fluid being studied, it is a well accepted consensus that hypotensive shock is typically accompanied by a release of catecholamines from the adrenal medulla and norepinephrine-producing cells.

Egdahl (1959) demonstrated a very small increase of epinephrine and norepinephrine output in adrenal vein plasma when dogs were given LPS in small fever-producing doses. Larger increases in catecholamine output occurred with shock-producing doses. Nykiel et al. (1959), Rosenberg et al. (1961) and Spink et al. (1966), using more sophisticated methods, identified the increase as being predominantly one of epinephrine. These increases did not occur in dogs with prior cervical spinal cord transection or adrenalectomy. Griffiths et al. (1972) reported a rise in norepinephrine in peripheral vein plasma from 0.26 to 2.3 ng/ml before death in dogs studied during rapidly lethal endotoxin shock.

Endotoxin shock in rabbits was also associated with increased plasma and urinary values of epinephrine, and norepinephrine to a lesser extent; LPS administration partially depleted the adrenal medulla of its hormones (Serafimow, 1962; Heiffer et al., 1958, 1959).

During experimental infections, plasma epinephrine has been found to increase in rabbits with tetanus (Busila et al., 1971). In contrast, rats with acute *Trypanosoma cruzi* infections showed a virtually complete disappearance of norepinephrine from the myocardium (Machado et al., 1978), apparently as a result of parasite-induced myocarditis.

B. *Studies in man*

Urinary or plasma catecholamines have seldom been measured during infectious diseases of man. Because of the technical difficulties of these hormonal measurements, urinary vanillylmandelic acid (VMA) values have sometimes been substituted as an indirect method for evaluating catecholamine metabolite output. As an example, Gruchow (1979) collected the urine output over a 4-week period from a large number of university student volunteers for daily measurements of VMA. During this period, 34 volunteers reported a common cold or flu-like illness. The available longitudinal data permitted a study of these illness periods and showed a tendency of VMA values to be slightly in excess of the normal baseline control range for the 3 days preceding the onset of respiratory symptoms and then to fall to, or below, baseline values on the first 2 days of illness.

In a similar study of military trainees, Mason et al. (1979) collected daily urine output to measure urinary catecholamine excretion values. An acute

severe adenovirus-4 respiratory illness occurred in 12 subjects. Daily group mean values for urinary epinephrine ranged from 9.9 to 12.0 $\mu\text{g}/\text{day}$ during the week preceding these illnesses, increased to 13.0 $\mu\text{g}/\text{day}$ the day fever began, and then ranged between 15.2 and 16.8 $\mu\text{g}/\text{day}$ during the next 5 days. Values for urinary norepinephrine excretion followed the same general trend, with group mean values for the 7 preillness days falling between 36 and 44 $\mu\text{g}/\text{day}$. Excretion increased to 48 μg on the first day of fever and then values ranged between 52 and 65 $\mu\text{g}/\text{day}$ during the next 4 days. Occasional sporadic increases in the daily excretion of these hormones were noted in individual patients during the week preceding illness.

These relatively modest increases in urinary catecholamine excretion during self-limited brief infections are consistent with the observations of Russian workers (Kolesov, 1967; Frakun, 1966) who reported slightly increased urinary catecholamine excretion values in 35 adults with dermal infections and in 22 children with pneumonia. Kats (1964) reported increases in blood epinephrine values in 71 children with bacillary dysentery. Increases in plasma concentrations of both epinephrine and norepinephrine have also been reported in surgical or burned patients who develop gram-negative bacterial sepsis and shock (Wilmore et al., 1974a, b; Carpentier et al., 1979).

IV. FUNCTION OF THE THYROID AND ITS HORMONES

Thyroid gland structure is often altered by fatal infections in man or experimental animals, with depletion of colloid and hyperplasia of acinar cells suggesting increased secretory activity (Shambaugh and Beisel, 1967b). On the other hand, physiological measurements show that glandular secretory functions may diminish somewhat during the early febrile stages of an acute infectious process. Concurrently, however, the rates of uptake and metabolism of thyroid hormones by peripheral body cells are generally accelerated (Wartofsky, 1974), and at the same time a greater percentage of T_4 is converted within cells to rT_3 rather than to T_3 (Chopra et al., 1975). Acute infections may even precipitate hypothyroidism and myxedema in patients with a marginal thyroid gland secretory capacity (Hausmann and Karlish, 1961). While the metabolic activity of body cells is accelerated during fever, there is no evidence that thyroid hormones participate directly in mechanisms that initiate or control the febrile response.

Many infection-related changes observed in thyroid gland function and in the distribution, turnover and metabolism of thyroid hormones are similar to those precipitated by trauma, surgery, or other acute illnesses of man. In brief, relatively mild infections, a longitudinal progression of subtle thyroidal changes emerge which tend to produce, overall, a biphasic pattern of response (Shambaugh and Beisel, 1967b). This is characterized by: (a) an early increase in rates of thyroid hormone utilization or cellular degradation in peripheral tissues; (b) a delay in TSH and thyroid gland responses to declining concentra-

tions of thyroid hormones in plasma; (c) a rebound of thyroid function during the convalescent period which may temporarily overshoot normal plasma hormone values; and (d) a final return to preillness equilibrium.

Such a concept must remain speculative at present, for relatively few prospective studies (Shambaugh and Beisel, 1967b; Wartofsky et al., 1972, 1977; Wartofsky and Earll, 1972; Lutz et al., 1972) have been conducted throughout the entire longitudinal course of acute infectious illnesses in man. Further, not all reported findings have been identical, even within groups of concurrently studied volunteer patients (Lutz et al., 1972). Some of this confusion about thyroidal responses can be ascribed to differences in: (a) the type of infection under study; (2) the severity and duration of illness; (c) the tests chosen for study; (d) the methods selected for conducting a test; and (e) the variability among animal species used for experimental studies (Gerwing et al., 1958; Wartofsky, 1974). Nevertheless, the conceptual understandings of thyroidal responses during a generalized infection must focus on two separate questions (Wartofsky, 1974). What factors control or influence the alterations in thyroid hormone distribution and metabolism among peripheral tissues during infection? and, what factors influence the regulatory controls for thyroid gland activity and responsiveness?

In a situation analogous to that of adrenal gland destruction, various forms of acute bacterial thyroiditis or antithyroidal immunological reactions during subacute thyroiditis following some virus infections can lead to fibrosis of the thyroid gland and impair its functional capabilities.

A. *Peripheral thyroid hormone metabolism*

Fractional T_4 turnover appears to be accelerated at the onset of acute bacterial and virus illnesses in man and some experimental animals (Wartofsky, 1974; DeRubertis and Kosch, 1975). Fractional T_3 turnover also increases in some patients (Gregerman and Solomon, 1967). Concentrations of rT_3 increase in plasma (Chopra et al., 1975; Burger et al., 1976). These changes are accompanied either by a decline in protein-bound iodine (PBI) values in plasma (Shambaugh and Beisel, 1966, 1967b; Lutz et al., 1972) or unchanged PBI values (Gregerman and Solomon, 1967). PBI values may then rebound to higher than normal values during early convalescence before eventually returning to preillness baseline values.

No clear-cut or consistent patterns of response have been defined for total T_4 concentrations in plasma, although the small fraction of T_4 that is not bound to plasma proteins will generally increase. On the other hand, T_3 values consistently decrease in plasma (Bermudez et al., 1975; Wartofsky et al., 1977; Kaptein et al., 1978) while rT_3 increases (Chopra et al., 1975; Burger et al., 1976; Wartofsky et al., 1977). The reason for an increased formation of the inactive metabolite, rT_3 , remains uncertain.

The rates of T_4 clearance from plasma increased in bacterial infections of rats

(Shambaugh and Beisel, 1966) and monkeys (DeRubertis and Woeber, 1972, 1973) as did T_4 clearance rates in monkeys (Woeber, 1971). The peripheral disposal of T_4 was also accelerated 2-fold in monkeys with yellow fever, a lethal virus infection. In contrast, accelerated T_4 disposal did not occur in monkeys with virulent Venezuelan equine encephalitis virus infection (DeRubertis and Kosch, 1975) even though an attenuated strain of the same virus caused an increase in the percentage of free unbound T_4 in the plasma of man (Shambaugh and Beisel, 1967b).

Changes in T_4 clearance have been inconsistent during experimentally induced bacterial infections in volunteers (Lutz et al., 1972). Kinetic studies of T_4 utilization during malaria have shown slowed rates of both clearance and fractional disappearance from plasma and a diminished rate of daily T_4 disposal (Wartofsky et al., 1972). The slowing of T_4 utilization in the patients with malaria instead of an infection-induced acceleration has been attributed to an impairment of hepatic function. Hepatic degradation of T_4 is normally an important component of the peripheral cellular metabolism of this hormone.

1. *Factors influencing T_4 metabolism*

Altered rates of T_4 disposal can be influenced by two major factors. These are, first, changes in the capacity of T_4 -binding proteins in plasma which serve to retain the hormone as a bound ligand, and, second, altered rates of uptake and disposal of T_4 by body cells including, importantly, cells of the liver and kidneys' parenchyma and fixed or mobile cells with phagocytic functions.

Diminished concentrations of both thyroxine-binding prealbumin and thyroxine-binding globulin have been reported during acute infections in man and experimental animals (Harvey, 1971). While this change should, conceptually, increase the percentage of free unbound T_4 available for uptake by body cells, observed alterations in T_4 kinetics could not, in any reported study, be attributed directly to concurrently measured changes in T_4 binding to plasma proteins (Lutz et al., 1972; DeRubertis and Woeber, 1973).

An increased hepatic uptake of T_4 has been observed in monkeys with salmonella or coliform gram-negative sepsis, but not in monkeys with pneumococemia (DeRubertis and Woeber, 1972, 1973). Impaired hepatic uptake of T_4 has been postulated to account for the difference in T_4 kinetics between malaria and most other infections (Wartofsky, 1974). Hepatic clearance or kinetics of T_4 disposal have not been studied during hepatitis, but severe liver damage in monkeys with lethal yellow fever infections did not prevent an acceleration of T_4 disposal (DeRubertis and Kosch, 1975). No change in the renal handling of T_4 has been reported during infection. In contrast, an increased T_4 uptake from plasma by cells engaged in phagocytic activity may have an important role in T_4 disposal, especially during pyogenic bacterial infections.

2. *Thyroid hormone participation in phagocytic processes*

The neutrophilic peroxidase, myeloperoxidase, has potent in vitro antimicro-

bial activity against bacteria, fungi, viruses and mycoplasma when combined with hydrogen peroxide and an oxidizable ionic halide cofactor, such as iodide, bromide, chloride, or thiocyanate. Of these, the conversion of iodide to iodine is the most potent in terms of its bactericidal capacity. Klebanoff and Green (1973) postulated that such a bactericidal system might function in vivo in activated neutrophils, and, further, that thyroid hormones within the cells might serve to supply the necessary iodine.

Human neutrophils convert T_4 into both T_3 and rT_3 in association with a sub-cellular $27\,000\times g$ particulate fraction which displays enzyme characteristics and an SH-group requirement (Woeber, 1978). Under resting conditions, human neutrophils degrade T_4 slowly, but this activity is markedly accelerated if the cells engage in phagocytic activity (Woeber and Ingbar, 1973). Most of the iodide liberated from T_4 and T_3 can be recovered in monoiodotyrosine or as iodine. The iodine is fixed in cytoplasmic sites which contain ingested bacteria. When stimulated by phagocytic activity, neutrophils and macrophages take up additional T_4 from the surrounding media. Although neither the superoxide radical nor hydrogen peroxide plays a major role in stimulating the deiodination of thyroid hormones, peroxide appears to be more important than superoxide in subsequent bacterial iodination.

A so-called experiment of nature amplifies this concept about the role of phagocytic cells in thyroid hormone degradation. The leukocytes of patients with chronic granulomatous disease are deficient in myeloperoxidase activity and these cells degrade thyroid hormones poorly during or after phagocytic stimulation (Klebanoff and Green, 1973).

DeRubertis (1974) showed that deiodination of T_4 by leukocytes from septic monkeys was significantly enhanced, with inorganic iodide being the predominant product of T_4 degradation. Although the deiodination of thyroid hormones appears to explain, in part, the acceleration of T_4 metabolism observed during some acute infections, it remains uncertain as to which cells are responsible for this. Because accelerated T_4 disposal occurred in monkeys with bacterial sepsis despite the fact that their peripheral white blood cell populations had been depressed by prior X-ray irradiation, DeRubertis and Kosch (1975) postulated that fixed tissue macrophages might be playing a role in both bacterial infections and certain viral ones such as yellow fever.

B. *Thyroid gland function*

1. *Iodide uptake*

The thyroidal uptake of ^{131}I was reduced in rats during acute pneumococcal sepsis, but not in mice or guinea-pigs infected with the same bacterial inoculum (Shambaugh and Beisel, 1966). The thyroidal uptake of ^{131}I in septic rats was also impaired despite the use of injected TSH as an additional stimulus.

2. Thyroidal ^{131}I release

The rates of release of thyroidal ^{131}I were slowed in rats with gram-positive bacterial infections (Reichlin and Glaser, 1958; Shambaugh and Beisel, 1966) and in rats, mice, and rabbits inoculated with LPS (Gerwing et al., 1958). In contrast, thyroidal ^{131}I release was increased in guinea-pigs and monkeys given LPS. Impaired release could be restored by TSH in LPS-inoculated rats, mice and rabbits.

Wartofsky et al. (1972) found that the rate of thyroidal release of previously administered ^{131}I was reduced in patients with acute malaria, but it then rebounded during convalescence. However, the accelerated peripheral T_4 turnover in the presence of unchanged PBI values in a large group of patients with acute bacterial pneumonia led Gregerman and Solomon (1967) to conclude that thyroidal release of T_4 must have been accelerated.

Wartofsky and Earll (1972) found that the release from the thyroid gland of non- T_4 iodine was also suppressed during malaria and returned toward control values, but with no rebound, during early convalescence. This observation suggests that any convalescent period rebound of PBI values is due to the actual secretion of hormonal iodine.

3. Pituitary controls

The failure of thyroidal T_4 release to increase quickly in the presence of an infection-induced acceleration in the peripheral disposal of T_4 has been ascribed to a sluggish response of hypothalamic-pituitary control mechanisms involving thyroid-releasing factor (TRF) and TSH (Wartofsky et al., 1977). The early convalescent period rebound of PBI has also been ascribed to a delayed pituitary response. Although a diminished TSH response could, in theory, be explained by an infection-induced increase in circulating cortisol concentrations, Reichlin and Glaser (1958) found comparable reductions in ^{131}I release if a bacterial infection was induced in adrenalectomized rats.

No studies have reported a rise in plasma TSH concentrations during infection, but reductions have been reported in elderly patients with septic shock (Kapstein et al., 1978) and in young adults with malaria (Wartofsky et al., 1977). The patients in the latter study, however, showed a normal response to injected TRF, with TSH values increasing rapidly in plasma to peak values which plateaued between 15 and 30 min after TRF was given.

C. Thyroidal membrane receptors for bacterial toxins

The recent finding that TSH would react with thyroid cell surface membrane ganglioside receptors suggested a mechanism of action for TSH analogous to that of cholera toxin (Ledley et al., 1977). Purified tetanus toxin binds to thyroid plasma membranes in a manner that exhibits time, pH and salt dependencies similar to those for TSH. This binding of tetanus toxin can be blocked, or 'chased', by an excess of either TSH or cholera toxin (Ledley et al., 1977). Rat

thyroid tumor cells with a known defect in TSH receptors are also defective in their ability to bind tetanus toxin (Habig et al., 1978).

The clinical significance of these observations remains uncertain, for no studies of thyroid function have been reported in patients with tetanus or cholera. To determine if tetanus toxin altered the hormonal function of the thyroid gland *in vivo*, this curious phenomenon was studied in mice with methods identical to those used for the bioassay of TSH activity. One minimal lethal dose of tetanus toxin, given *s.c.*, did cause a significant release of thyroidal radioactive iodine in mice, and was therefore analogous to TSH in its ability to stimulate the thyroid gland (Habig et al., 1978). This observation led to suggestions that the 'sympathetic overactivity syndrome' seen in some patients with tetanus, or an infection-induced 'thyroid storm' in patients with Graves' disease, might be triggered by direct toxin-induced stimulation of hormonal release from the thyroid gland.

V. PITUITARY RESPONSES

A number of pituitary hormones participate in the host responses to infection. Little is known, however, about the mechanisms that control the altered patterns of pituitary hormone release, or how the higher hypothalamic centers are informed that an infectious process has been initiated in some distant tissue.

Because glucocorticoid secretion is stimulated early in either infection or endotoxemia, ACTH release must be a preceding event. A few actual measurements of ACTH concentrations in plasma tend to confirm this probability during infection (Takebe et al., 1966; Zimmermann et al., 1965a). ACTH is also released following the inoculation of normal individuals with fever-producing doses of LPS (Rayfield et al., 1977).

Single studies describe an infection-induced release of several other anterior pituitary hormones. The administration of thyrotropin-releasing hormone to volunteers with falciparum malaria stimulated a normal release of TSH, and a somewhat greater than normal release of prolactin (Wartofsky et al., 1977). Severely ill postmenopausal women, including several with bacterial sepsis, were found to have significantly depressed values for luteinizing (LH) and follicle-stimulating hormones (FSH), with a loss of characteristic pulses in plasma concentrations of these hormones which is typically seen in age-matched normal controls (Warren et al., 1977). LH was more severely depressed than FSH, and LH did not return to baseline values as promptly upon recovery as did FSH.

Considerably more information is available about infection-stimulated increases in plasma growth hormone values as well as occasional examples of an inappropriate secretion of antidiuretic hormone (ADH) from the posterior pituitary gland in certain types of infection.

A. *Growth hormone*

The secretion of growth hormone following stimulation by small, fever-producing doses of bacterial endotoxin is one of the most sensitive indicators of anterior pituitary gland function in man (Frohman et al., 1967; Kimball et al., 1968).

Increased concentrations of growth hormone in plasma have been observed in a variety of clinical infections including sandfly fever (Beisel et al., 1968; Rayfield et al., 1973; Alluisi et al., 1980), attenuated viral vaccine fevers and typhoid fever (Winnacker et al., 1969). Growth hormone increases occur at the time of, or somewhat before, the onset of fever. Increases are not persistent throughout the entire course of fever and may be minimal in subacute infections such as typhoid fever, or absent in chronic infections such as tuberculosis (Zimmermann et al., 1965b). No attempts have been made during these acute infections to determine if growth hormone secretion remains pulsatile as in normal persons or if plasma values undergo a typical normal increase with the onset of sleep.

A number of studies have been conducted in rhesus monkeys in an attempt to define the mechanisms leading to augmented growth hormone secretion. In longitudinal studies, the increase in plasma growth hormone values noted early in pneumococcal bacteremia did not persist more than a day or two; further, the increase could be enhanced by i.v. infusions of arginine or insulin and diminished by anesthesia or α -adrenergic blockage using phenoxybenzamine (Winnacker, 1970, 1971).

Rayfield et al. (1973) observed an unexpected, or paradoxical, abrupt increase in plasma growth hormone values which was triggered by an i.v. infusion of glucose in volunteers with acute sandfly fever. A similar response was found in monkeys infected with *Salmonella typhimurium* (Rayfield et al., 1974). These glucose-stimulated increases were suppressed in pneumococemic monkeys pretreated for 1 week with chlorpromazine but not by acute α -adrenergic blockade with phentolamine (Rayfield et al., 1974).

Winnacker (1970, 1971) found that fever alone, if induced in monkeys by physical means, would not trigger growth hormone release. In contrast, a transfusion of sterile plasma obtained from febrile monkeys with pneumococcal sepsis, or preparations of endogenous pyrogen obtained in vitro from phagocytizing monkey leukocytes, were able to initiate both a febrile response and growth hormone release in healthy recipient monkeys.

B. *Antidiuretic hormone*

An expansion of the extracellular fluid volume in the presence of falling sodium concentrations and progressive hypo-osmolality constitute a dangerous complication of some infectious diseases. This combination of physiologic abnormalities during infection has been ascribed to an inappropriate secretion of antidiuretic hormone (Kaplan and Feigen, 1978).

This problem occurs most often during infections that become localized in the central nervous system (Nyhan and Cooke, 1956; Mangos and Lobeck, 1964; White et al., 1969; Kaplan and Feigen, 1978), but it may occur also during some pulmonary infections and in a few of the more generalized infections such as Rocky Mountain spotted fever (Weiss and Katz, 1965; Sexton and Clapp, 1976).

Few data document actual changes in plasma values of antidiuretic hormone and none are available to compare the levels of antidiuretic hormone with those of aldosterone during the course of illness. Kaplan and Feigen (1978) assayed arginine vasopressin in the plasma of children with a variety of acute infections and found that their values were not significantly different from those of normal children. These normal values ranged from 0.0 to 1.8 $\mu\text{U/ml}$. In contrast, 17 patients with bacterial meningitis and a comparable length of acute illness showed arginine vasopressin values ranging from 0.5 to 7.6 $\mu\text{U/ml}$ in plasma, with a group mean value significantly higher than that recorded for either the control group or the group with diverse infectious illnesses (Kaplan and Feigen, 1978).

VI. PANCREATIC ISLET HORMONES

Altered glucose metabolism is prominent among the host responses to infection. Diabetic subjects typically show increased hyperglycemia and glycosuria whenever they develop an acute infection, and they exhibit an apparent insulin resistance. After undergoing an initial brief increase in blood glucose values, experimental animals with endotoxemic shock typically develop severe terminal hypoglycemia along with a depletion of body glycogen stores. The metabolic aspects of glucose production and utilization during infection or toxemia are described in other chapters of this text. In addition to the influences of substrate availability and the functional competence of gluconeogenic machinery within host cells, a large number of hormones participate in the glucoregulatory aspects of infection. These hormones include the adrenal glucocorticoids, catecholamines, thyroidal hormones, growth hormone, and importantly, insulin and glucagon.

Infection and bacterial toxemia generally stimulate an unusual pancreatic islet response in that both insulin and glucagon values are increased simultaneously. The factors accounting for the dual increases in both of these islet hormones have not as yet been clarified, but several possible control mechanisms exist. An intact anterior pituitary gland is clearly required to permit an increase in pancreatic insulin secretion during experimentally induced infection (Neufeld et al., 1980). Hormone-like substances (leukocytic endogenous mediator or endogenous pyrogen) released into plasma by activated phagocytic cells may also help regulate pancreatic islet hormone secretion (George et al., 1977). Preparations containing partially purified quantities of these phagocytic cell products stimulate an acute increase in both insulin and glucagon pro-

duction when injected in vivo in normal rats. However, it remains unclear as to whether the release of pancreatic hormones occurs in response to a direct stimulation of the islets by phagocytic cell products, or indirectly after an initial stimulation of the hypothalamus (Beisel and Sobocinski, 1980).

A third factor that could influence plasma insulin values during infection is an alteration in insulin receptor numbers and/or affinities on the surface membranes of peripheral body cells (Shimizu et al., 1980; Anderson and Merrill, 1980). Any infection-induced response that reduces or inhibits the binding of insulin to cell surface receptors would create a form of apparent insulin resistance. And lastly, acidosis or a markedly altered plasma protein profile during infection could introduce other poorly understood inhibitory factors that might reduce the normal ability of insulin to influence carbohydrate, protein and fat metabolism.

A. *Insulin*

As first shown in volunteers with respiratory tularemia, fasting plasma concentrations of insulin increased slightly with the onset of symptomatic illness (Shambaugh and Beisel, 1967a). An i.v. infusion of glucose given at that time stimulated a brisk rise in plasma insulin to higher than normal values, followed by a slower than normal return toward fasting baseline concentrations. The normal values for the same individuals in this study were determined during glucose infusions given before exposure to the infecting bacteria and again following full recovery. The disappearance kinetics of infused glucose and secreted insulin early in acute tularemia thus resembled insulin kinetic patterns typical of patients with mild adult-onset diabetes.

Studies during experimental infections in laboratory animals also showed increased concentrations of immunoreactive insulin in plasma. Acute pneumococcal sepsis in rhesus monkeys was accompanied by mild, relative hyperinsulinemia following i.v. administration of glucose (George et al., 1974). Portal vein concentrations of insulin rose significantly in rats with pneumococcal infection (Zenser et al., 1974; Curnow et al., 1976) as did values in peripheral blood (Kaminski et al., 1979; Neufeld et al., 1980). Similar modest increases in insulin values were also seen during a gram-negative infection of rats (Curnow and Rayfield, 1973; Ryan et al., 1974).

In contrast to the tendencies for plasma immunoreactive insulin values to increase during acute infections in man, monkey and rat, Cryer et al. (1972) found significant hypoinsulinemia in baboons 15 min after a massive i.v. infusion of living *E. coli* which generally produced death in less than 2 h. This fall in plasma insulin values was prevented by α -adrenergic blockade with phentolamine. Insulin responses to i.v. infusions of glucose were not tested in this study. The glucose response of the baboons in this study included an initial hyperglycemia but lacked the severe terminal hypoglycemia which typifies most overwhelming septic infections. The differences in the directions of plasma insulin

and glucose change from those reported by other groups may be species related, or they may possibly be due to the overwhelming nature of the bacterial challenge in this baboon study with its very rapid time-to-death (Cryer et al., 1972).

Gram-negative bacterial endotoxin has been used to study insulin responsiveness in both man and experimental animals. Following endotoxin administration in fever-producing doses, normal subjects developed basal and glucose-stimulated hyperinsulinemia (Rayfield et al., 1977). Dogs given endotoxin in lethal doses, followed by a glucose infusion to prevent hypoglycemia, developed a marked hyperinsulinemic response to the infused glucose (Spitzer et al., 1976; Blackard et al., 1976). Since insulin disappearance rates from plasma remained normal, the marked hyperinsulinemia could not be explained by an impaired degradation of insulin. Further, the hyperinsulinemia after glucose infusion in endotoxemic dogs was not inhibited by β -adrenergic blockade.

Relatively little information is yet available concerning the serial progression of changes in cellular insulin receptor numbers or binding affinities during the course of an infection. Shimizu et al. (1980) found that *in vitro* infections of cultured human amnionic cells with herpes simplex or vesicular stomatitis viruses produced a 50% decrease in receptor cell numbers with no change in receptor affinity. This decrease in receptor numbers occurred early in the infection (4–12 h) and at a time when viral antigens were being inserted into the plasma membrane of the infected cells. Since other viruses, such as encephalomyocarditis, that did not insert new antigens into cellular membranes also failed to alter cell receptor numbers, Shimizu et al. (1980) suggested that direct virus-induced changes in the plasma membranes could be masking or displacing the insulin receptors. In an *in vivo* study in man, Anderson and Merrill (1980) demonstrated a decreased insulin binding by human mononuclear cells obtained from peripheral blood at the onset of symptomatic illness in sandfly fever in volunteers. This decrease was associated primarily with a loss of cellular insulin receptors during the illness, but one of three volunteers studied also showed an increase in receptor affinity. An increase in the plasma insulin-to-glucose ratio observed during sandfly fever implied that insulin resistance was present and could explain the transient intolerance to carbohydrate which appears typical in acute infections of man. On the other hand, the accelerated gluconeogenesis and expanded extracellular glucose pool during infection serve to provide body cells with substrate required by the increased metabolic rates due to fever.

Infectious diseases which localize within the pancreas may cause sufficient destruction or damage to islet cells that hormonal function is subsequently impaired. Diabetes can therefore be a secondary consequence of severe bacterial pancreatitis, or viral infections such as mumps (Dacou-Voutetakis et al., 1974). Infections in laboratory animals with encephalomyocarditis, Coxsackie, or virulent Venezuelan equine encephalomyelitis viruses have been shown to cause islet cell damage and a persistent deficiency in insulin secretion (Craig-

head and Steinke, 1971; Coleman et al., 1973; Rayfield et al., 1976). Since functional changes in islet cell secretion of its hormones and in blood glucose kinetics occur transiently during acute infections, careful studies are required to show that any given virus is truly diabetogenic in man. Nevertheless, infections due to pancreatotropic viruses remain a very real possibility as an initiating or contributing factor in the pathogenesis of juvenile diabetes.

B. *Glucagon*

When immunoreactive glucagon is measured in plasma, increased concentrations are consistently found during acute infectious diseases. Rocha et al. (1973) initially described unusually high concentrations of glucagon in the plasma of nondiabetic patients with various bacterial infections. This finding was quickly confirmed in virus infections also (Rayfield et al., 1973; Anderson and Merrill, 1980) and in additional patients with severe bacterial sepsis (Duff et al., 1975). Hyperglucagonemia in burned patients is exaggerated further if they become septic (Wilmore et al., 1974a).

Rocha et al. (1973) also found hyperglucagonemia in dogs with experimental pneumococcal pneumonia. Similarly, infections with the pneumococcus also initiate fasting hyperglucagonemia in monkeys (George et al., 1974) and rats (Zenser et al., 1974; Kaminski et al., 1979). The infection-induced increase in plasma glucagon values in man, monkey and rat declines promptly in response to an i.v. infusion of glucose (Rayfield et al., 1973; George et al., 1974; Zenser et al., 1974). Zenser et al. (1974) showed further that the increase in hepatic cyclic AMP which accompanied hyperglucagonemia in infected rats could also be suppressed by glucose administration. On the other hand, as infection progressed in rats, cyclic AMP responsiveness to glucagon became blunted, possibly in relationship to plasma membrane injury in hepatic cells. Zenser et al. (1974) postulated, therefore, that relative resistance to glucagon may develop during infection as it does with insulin.

Hyperglucagonemia is also induced by giving bacterial endotoxin to man or experimental animals. Rayfield et al. (1977) found that the administration of fever-producing doses of LPS to healthy volunteers led to dramatic and rapid increases in their plasma glucagon concentrations. This increase preceded the onset of fever and was reversed with a precipitous decline in glucagon values when the subjects were given an i.v. infusion of glucose. In an identical study in diabetic subjects who were receiving 4 U/h of regular insulin, the glucagon response after similar doses of LPS was quite prominent, but values increased less rapidly, peaked at lower concentrations and responded less rapidly to i.v. infusion of glucose (Rayfield et al. 1977). A 10-fold rise in immunoreactive plasma glucagon was also observed in dogs given endotoxin (Blackard et al., 1976).

C. Molar insulin-to-glucagon (I/G) ratios

Acute infection and induced endotoxemia are unique in that basal concentrations of insulin and glucagon are both increased, although the molar increase in glucagon is relatively greater. These combined responses have resulted in a consistent decline in the I/G ratio during acute infections (Rocha et al., 1973; George et al., 1974; Zenser et al., 1974; Wilmore et al., 1974a).

A fall in the plasma I/G ratio also occurs during fasting, but this is due to a different set of response patterns by both insulin and glucagon in comparison to those seen during infection (Neufeld et al., 1980). Nevertheless, the declining I/G ratio typifies the type of response which is typical of catabolic illnesses (Unger, 1971).

VII. IMPLICATIONS OF ENDOCRINE RESPONSES

The molecular nature of hormonal actions is still being defined at the cellular level, and it cannot yet be said with certainty exactly how the complex pattern of infection-induced hormonal responses may serve to influence host survival. Normal endocrine responsiveness would appear to be beneficial to the host. Clinical experience in man and some studies in experimental animals suggest that host resistance is diminished during diseases which exhibit either a chronic excess or a chronic deficit of hormonal secretions by either of two major endocrine organs, the adrenals and the thyroid. Infectious illnesses exhibit increased severity and may become life threatening in patients with Addison's disease, Cushing's disease, or hypo- or hyperthyroidism.

Certain of the hepatic enzymes can be induced by glucocorticoid hormones, the synthesis of some hepatic proteins requires the permissive presence of glucocorticoids, while still other proteins can be synthesized by the liver in the total absence of these hormones (Thompson et al., 1976). The glucocorticoids also are known for their lympholytic effects, but no role for a corticoid-lymphocyte interaction has as yet been identified in terms of a defined molecular effect on immune system responsiveness to antigens introduced by infectious microorganisms.

Controlled metabolic balance studies have clearly shown that the transient, relatively small increase in cortisol secretion during infection could in no way explain the magnitude or duration of protein catabolism and body nitrogen loss seen during infection (Beisel et al., 1967a). On the other hand, Rocha et al. (1973) demonstrated that a series of glucagon injections in dogs would cause a marked catabolic response with rapid losses of body weight and body nitrogen. Rocha et al. (1973) postulated that glucagon responses during an acute infection would contribute importantly to the acceleration of gluconeogenesis and the deamination of amino acids to provide sufficient carbon-chain substrate to allow an increase in hepatic glucose production. A catecholamine response

during sepsis would also help amplify the increased hepatic release of glucose (Wilmore et al., 1974b). Insulin secretion during infection appears to contribute to diminished ketogenesis (Neufeld et al., 1980).

On the other hand, the role of increased growth hormone secretion in infection-stimulated metabolism is quite uncertain. Although plasma growth hormone concentrations may increase, children and adolescent patients consistently show a transient cessation of growth in association with the catabolic losses of body weight and nitrogen which typify acute and chronic infections.

Perhaps the most clearly defined physiologic actions of hormones during infectious illnesses are those due to aldosterone and antidiuretic hormone effects on renal tubule cells. Their actions can account reasonably well for the renal retention of salt and sometimes of water which occur during certain infections.

Another major uncertainty is related to the nature of the control mechanisms which may trigger, sustain and eventually terminate the many interrelated hormonal responses seen during infection. These controls could involve a large variety of humoral substances secreted by cells throughout the body. Although the secreted substances are not traditionally thought of as hormones, they do stimulate responses in distant tissues. Such substances include endogenous pyrogen, leukocyte endogenous mediator, histamine, interferon, angiotensin, myocardial depressant factor, more than a dozen brain neurotransmitter peptides, and the various prostaglandins, and, acting as secondary intracellular messengers within cells, the cyclic nucleotides (Kampschmidt, 1974, 1980; Dey et al., 1974; Pettit et al., 1978; Snyder, 1980; Beisel and Sobocinski, 1980). Very little is known about the mechanisms that control or initiate responses at the hypothalamic level, and how these responses might in turn generate direct neural messages to distant tissues or the release of neurosecretory hormones.

VIII. HORMONES IN THERAPY

With the growing availability of ACTH, cortisone and cortisol, and the publication of Selye's hypothesis (1946), 'steroid therapy' was widely used as an adjunct in the treatment of infectious illnesses during the 1950's. As pointed out by Migeon et al. (1967), over 1000 favorable but uncontrolled reports appeared in medical literature before the practice of using steroids for suppression of fever and other symptoms during acute infections was generally abandoned. On the other hand, a patient without functioning adrenocortical cells needs a physiological-range increase in daily doses of steroid replacement therapy during periods of acute infectious illnesses.

In this regard, patients with acute infectious illnesses cause two different types of therapeutic problems for those who specialize in endocrinology. The first deals with the need to alter hormonal treatment regimens if an infection occurs in a patient with a known endocrinopathy. Physiologic increases (1—3-

fold) in the usual doses of hormone replacement therapy are desirable in patients with diabetes, adrenal insufficiency, or hypothyroidism. An increase in growth hormone therapy is not generally given to children with pituitary dwarfism, but may be of value. Patients under therapy for hyperthyroidism should be watched with great care and hospitalized for emergency management of thyroid storm if hyperthermia begins to develop. A different set of problems emerges in the treatment of infected patients without a known endocrine problem. Diagnostic test abnormalities may be due to a physiological endocrine response to the infection rather than to a true 'disorder.' On the other hand, two true medical emergencies may arise, adrenal apoplexy which demands prompt and adequate steroid-supportive therapy, and inappropriate ADH syndrome which requires a very careful restriction of fluid and electrolyte input.

Limited numbers of studies in laboratory animals suggest that some new experimental combinations of hormone therapy may increase survival rates in certain infections (Bucher, 1976; Schole et al., 1978). Bucher (1976) found that the survival of mice given lethal doses of A-59 murine hepatitis virus was greatly prolonged if the mice were treated with infusions containing both insulin and glucagon, and, further, that 40% of the mice survived if given dual hormonal therapy. Schole et al. (1978) reported increased survival of animals with experimental bacterial or parasitic infections if they were treated at the right point of illness with a combination of corticosteroid and growth hormone. While these results are encouraging, they point out, primarily, the need for a better understanding of the role and importance of hormone production, metabolism and distributional changes during infection. Further, most forms of infection which occur in hospitalized patients are seen in the presence of diverse other problems such as trauma, burns, malignancies, radiation or immunosuppressive therapy, or generalized malnutrition. All of these factors must be brought into focus when evaluating the endocrine status of a severely ill patient.

Note

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

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