HORMONES AND HOST RESISTANCE TO INFECTION

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As biologic organization became increasingly complex during the evolutionary process, evidently survival value became attached to the development of hormonally mediated regulatory mechanisms. It would not be surprising to find that as mechanisms of resistance to infection also became more complex, these also came under hormonal influence to some degree. Thus, the study of the influence of hormones on mechanisms of resistance to infection may offer insights not only into immune processes but perhaps also into the means by which hormones regulate physiologic processes.

At present no completely satisfactory mechanistic description of the action of any hormone exists. The many attempts to demonstrate specific enzymatic changes in tissues in consequence of alteration in hormonal activity have provided ample evidence that many enzymatic activities are altered after the administration of various hormones to various hosts. However, direct and specific enzymatic responses to the action of hormones have been demonstrated in but one or two instances, and the general applicability of even these is far from clear. For example, the demonstration by Villee (30) of the stimulation by estrogen of DPN-dependent uterine transhydrogenase is one of the rare examples of a hormone-sensitive metabolic system operating *in vitro*. However, many potent estrogens do not participate in this hydrogen transfer system in a very active way and, at present, there is no way that the transhydrogenase reaction can explain, for example, the effect of estrogens on uterine growth, pituitary function, secondary sex characteristics, or thyroid binding protein of the blood. Ignorance of the mode of action of hormones both as to their general physiological effects as well as in relation to mechanisms of resistance to infection permits empirical statements only.

It would not serve the purpose of the present symposium to attempt to review in detail the diverse literature relating hormones to mechanisms of resistance to infection. Instead, in the discussion to follow, an attempt will be made to thread through some of the uncertainties of observation in relation to the influence of hormones on mechanisms of resistance to infection. A few recent observations in the author's laboratory will be added because they seem to provide possible bases for new looks at old problems.

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SUSCEPTIBILITY TO INFECTION IN DIABETES

In general, when a hormone plays an important homeostatic role throughout life, it is to be expected that deprival of this hormone will influence adversely the capacity of the host to withstand the onslaughts of harmful agents. This expectation, however reasonable, is not always satisfied. In diabetes mellitus, it is generally held, there is increased susceptibility to infection, and possible metabolic bases for this susceptibility have been suggested (5). A critical perusal of the literature, however, offers remarkably little evidence to support the initial assumption. There is no doubt that severe infections cause disturbances in carbohydrate, mineral, and other aspects of metabolism, and no doubt that infection superimposed on diabetes mellitus makes control of the diabetes more difficult, thereby constituting a threat to the individual's survival. Whether, however, the diabetic individual is successfully invaded by smaller numbers of infectious particles than is the nondiabetic, or permits greater multiplication of pathogens than does the nondiabetic may be seriously questioned.

It is clear that specific immune mechanisms are operative in diabetic patients and in diabetic experimental animals to just about the same degree as in nondiabetics (19–22). Some decrease in the bactericidal action of the blood of alloxan-diabetic animals has been reported but the data are not striking (4). In experimental bacterial infections, in alloxan-treated or pancreatectomized, chronically diabetic animals, no substantial diminu-

tion in resistance has been demonstrable (6, 20, 25). Only in the experiments of Elder and Baker (6), involving a fungal infection in rabbits, has there been clear evidence of increased susceptibility to infection during the experimental diabetic state. The diabetic animals were most susceptible during the state of ketosis which was present during the acute toxic state that occurs in rabbits shortly after alloxan has been injected. Whether this result indicates special growth requirements of the fungus, or suggests that certain ketone bodies interfere with the ordinary defensive mechanisms of the host, or simply reflects an acute toxic effect of alloxan that is unrelated to diabetes mellitus and that increases susceptibility to infection, requires further study. Certainly alloxan is toxic, apparently apart from its effect on the islets of Langerhans.

Clinically there is strongly suggestive evidence that diabetics have more surface infections than do nondiabetics, that they have more tuberculosis, and that they have more infections of the urinary tract (8, 20, 22, 26). However, when the causes of death in diabetic and nondiabetic patients were compared at autopsy by Robbins and Tucker (23), the incidence of pneumonia and of other infections was about the same in both groups, with the exception that pyelonephritis occurred more frequently in diabetics. Even the latter finding must be scrutinized carefully, however, in order to delineate the role of catheterization, of neurologic disease affecting bladder function, and of vascular degenerative disease affecting the kidney, before the finding can be accepted on solid grounds. The tendency of hospitals to collect diabetics, and to pay special attention to their problems, especially when infection is involved, is obvious. Small infections may aggravate existing diabetes and thus call attention to their presence in the diabetic. The need is great for careful studies that will separate the ability of diabetics to alter the rate of multiplication of pathogens from the effects of complications of diabetes in altering host resistance, and from the effect of infection in aggravating the diabetic state.

HYPOFUNCTION AND ABSENCE OF FUNCTION OF ENDOCRINE GLANDS AND RESISTANCE

The role of hypofunction of endocrine glands other than the pancreas in resistance to infection is also not easy to define. Two aspects of hypofunction must be considered: absolute hypofunction, either because of absence of the gland or because of interference with its activity; and relative hypofunction, in which the gland functions but does not release sufficient hormone to produce optimal adjustment in the host to circumstances causing increased hormonal output.

Relative hypofunction is much considered, but difficult to document. When specimens of blood were taken from over 100 patients with severe sepsis, all but two had levels of circulating corticosteroid greater than the normal range, and these two exceptions were in the high normal range. No blood levels in the Addisonian range have been encountered so far in our studies, even in patients with collapse due to sepsis, who were destined to die. The only exceptions were in patients with pre-existing Addison's disease (12). The increased levels of corticosteroid usually reflect impairment of the mechanisms for metabolizing steroid. In any event, there is little evidence to suggest relative insufficiency.

Absolute hypofunction of the adrenal cortex or the pituitary seems quite clearly to permit smaller numbers of infectious agents to multiply than would otherwise be the case in a given host (11, 12). Hypoadrenalism also increases susceptibility to toxic bacterial and other substances. However, hypoadrenalism interferes little if at all with phagocytic and specific antibacterial mechanisms (11, 20) and the apparent hazard to the host of hypoadrenalism may be related as much to increased susceptibility to the physiologic derangements (or toxic action) produced by the infection as it does to factors involving increased rates of microbial multiplication or more ready establishment of invading organisms.

It is useful, and probably mechanistically justified, to separate the physiological derangements accompanying an infection from the capacity of infectious agents to increase their numbers in a given host. Examples illustrating such a separation may be drawn from the literature involving the roles of the thyroid gland and the adrenal cortex in resistance to infection.

THYROID FUNCTION AND RESISTANCE TO INFECTION

Although the evidence is not completely secure, hypothyroidism tends to be associated with somewhat diminished resistance to infection and hyperthyroidism acts inconstantly in the opposite direction (19, 21, 23). Lurie and his associates

(13), using careful quantitative studies, showed that hypothyroidism, whether surgically or drug induced, permitted increased multiplication in the lungs of rabbits of inhaled human tubercle bacilli. These workers also showed that hypermetabolism induced by the administration of triiodothyronine or of thyroxine, but not that induced by dinitrophenol, was associated with diminished multiplication of the tubercle bacilli in most of the strains of rabbits studied (14). On the other hand, Smith and Dubos (28) using mice, and Reichlin and Glaser (21), who studied streptococcal pneumonia in rats, obtained apparently opposite data. The latter workers, in fact, were able to demonstrate an inverse relationship between the degree of thyroidal activity and the survival rate of the infected animals. However, as Smith and Dubos recorded, the pathogens did not multiply in their test animals, yet hyperthyroidism diminished the survival rate of their animals. The suggestion was made, therefore, that the toxic effect of the infection was less severe in hypothyroidism, and more severe in hyperthyroidism. Substantiation for this point of view is also found in observations that experimental hyperthyroidism increases susceptibility to bacterial endotoxin (16). Thus, in Lurie's experiments, the organisms seem to have been relatively nontoxic to the host, and hyperthyroidism seems to have inhibited bacterial multiplication without increasing the hazard of the toxic effect. It would appear that critical metabolic systems are less susceptible to attack when they are relatively quiescent, a concept with support in many biologic studies.

EFFECT OF ADRENOCORTICAL HORMONES ON RESISTANCE TO INFECTION AND TO ENDOTOXIN

Another example of the dissociation of toxic action of bacterial or host reaction products from other aspects of resistance to infection is found in the literature dealing with the adrenal cortex. It is generally agreed that both the hypoadrenal and the hyperadrenal states confer increased susceptibility to infection (12). This effect is illustrated in figure 1. Intact mice were given a uniform dose of specific antiserum sufficient to protect half of them against 50,000 pneumococci. Adrenalectomized mice, given the same amount of antiserum, were killed by only 1000 pneumococci. Replacement of the adrenocortical steroid restored the animals to their initial state

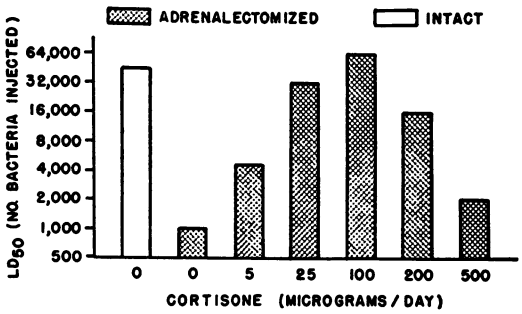

Figure 1. Effect of cortisone on pneumoccoccal infection in mice, all given same dose of specific antiserum; dose sufficient to protect 50 per cent of intact mice against 50,000 virulent pneumococci. Adrenalectomy markedly enhanced susceptibility to pneumococcal infection, as shown by the much lower LD_{50}. Cortisone (5 or 25 μg per day) partially restored resistance of adrenalectomized mice, whereas dose of 100 μg increased LD_{50} essentially to that of control mice. Larger doses of cortisone reduced resistance, as shown by decrease in number of pneumococci necessary to produce fatal infection.

of resistance, although the dose of steroid that provided optimal resistance proved to be about 4 times as great as the smallest dose that permits maximal growth of the mice. Still larger doses of steroid reduced the LD_{50} of the bacteria to levels similar to those observed for adrenalectomized animals. From the therapeutic point of view it may fairly be asked how much is the right dose in man, if too little and too much corticosteroid are equally harmful. No answer is at present available.

In contrast is the effect of replacement of corticosteroid in the animal being challenged with endotoxin. In this situation, protection increases progressively as the dose of steroid rises, so that even the intact animal is protected from the lethal effect of bacterial endotoxin by prior administration of corticosteroid. Although this protective effect of corticosteroid is seen only within narrow limits of dosage of endotoxin, it is nevertheless striking.

Since the anti-inflammatory and anti-endotoxic effects of corticosteroids appear to be different it might be reasonable to search for structural alterations in the steroid that might enlarge the differences. Table 1, taken from studies conducted with Brooke and Hechter (2), shows that dissociation of the anti-endotoxic and anti-in-

TABLE 1

Relative anti-inflammatory (glucocorticoid) and anti-endotoxic effects of steroids

Steroid	Anti-inflammatory	Anti-endotoxic
Cortisol	1.0	1.0
Corticosterone	0.5	0.7
Prednisone	3.5	0.7
Prednisolone	4.0	1.3
6-α-Methyl prednisone	5.0	30.0
11-Deoxycorticosterone	<0.1	0.1
11-α-OH-progesterone	<0.1	0.03

flammatory properties of corticosteroids is possible. For example, clinically and in experimental inflammations, 6-methyl prednisolone is about 5 times as active as is cortisol, but is about 30 times as active as cortisol as an anti-endotoxic agent. Whether this approach has ultimate clinical usefulness is not clear. The use of corticosteroids generally does not benefit the host in experimental infections due to endotoxin-producing bacteria (3), for the anti-inflammatory effect of corticosteroids generally predominates over the anti-endotoxic. It has been shown by many workers that the anti-endotoxic effect is demonstrable in mice, rats, and large rabbits, but is not seen in guinea pigs or dogs (12). Thomas (29) has demonstrated that corticosteroids in small rabbits act like the preparative dose of endotoxin in the generalized Shwartzman reaction, so that steroid-treated young rabbits respond to a single dose of endotoxin by the production of bilateral renal cortical necrosis. There are then reasons to suspect that the anti-endotoxic effect of corticosteroids may not be as useful therapeutically as might be hoped. It is too soon to state whether there is any benefit to be gained from the use of corticosteroids in clinical infections due to endotoxin-containing bacteria, but preliminary analysis of the data does not hold out much promise, save perhaps in tuberculosis (31), in which there is evidence to indicate an advantage to the use of corticosteroids along with antituberculous therapy.

Nevertheless it is possible that corticosteroids may be employed to separate the physiological consequences of an infection from the factors involving establishment and multiplication of the infectious agent in the host.

The preceding portion of this review may be briefly summarized with the statement that we know too little about what happens in nature and until our empirical observations become more securely established we cannot evaluate many of the experimental observations. A brief survey of the present knowledge of the relationship of hormones to resistance mechanisms will be attempted next.

RELATIONSHIP OF HORMONES TO MECHANISMS OF RESISTANCE

Of the major protein hormones, all arising from cells migrating originally from the alimentary tract, little is known about any possible relationship of parathyroid disease to resistance to infection, save as the urinary tract may be infected in consequence of calculous disease secondary to hyperparathyroidism. The role of the thyroid gland has been discussed in part already. No major influence of thyroidal activity on antibody responses, phagocytic mechanisms, or inflammation has been well documented, although the data of Lurie *et al.* (13) suggest some diminution in the antibody response in hypothyroid rabbits. Although increased demand for thyroid hormone may occur in infection and trauma, and it is conceivable that there may at times be relative thyroidal insufficiency, this has not yet been documented. There is little doubt that infections may precipitate thyroidal storms in hyperthyroidism, but this may simply represent aggravation of the underlying metabolic disturbance without reflecting any specific involvement of mechanisms of resistance.

Insulin deficiency has already been discussed.

Anterior hypophyseal hormones have not been implicated in mechanisms of resistance except through the trophic effects on end organs such as the adrenal cortex or the thyroid, hence no detailed discussion will be attempted, except for mention of somatotrophic hormone. This hormone has been shown to reverse certain metabolic changes induced by adrenocortical hormones and has reversed the adverse effect of corticosteroid in infection in a few experiments. However, the data are contradictory and this effect of growth hormone is far from uniform (11, 12).

Little need be said of the amine and small-molecule hormones arising from cells derived from the nervous system. No indications of important involvement of the neurohypophysis in mechanisms of resistance are recorded, save for

the hypothalamic link that is difficult to interpret. Epinephrine and norepinephrine are potent vasoactive substances with important therapeutic roles, but direct effects on mechanisms of resistance to infection do not seem to be of consequence.

The steroid hormones arise from cells derived from coelomic mesothelium and are made by the adrenal cortex and the gonads. The discovery of the unexpected and unexplained anti-inflammatory action of corticosteroids has stimulated much study. At present it is clear that corticosteroids in excess reduce the inflammatory response, presumably by decreasing permeability of the small vessels through which exudation occurs. Corticosteroids diminish the antibody response, alter reticulo-endothelial function, probably by delaying the rate at which the reticulo-endothelial system returns to normal phagocytic function after particles have been ingested by reticulo-endothelial cells. Corticosteroids also delay the rate at which mononuclear phagocytes can dispose of ingested particles. These hormones are also anti-endotoxic and antipyretic (11, 12).

In the case of the gonadal steroids, nature has performed a gigantic experiment, with striking changes occurring at different times in a normal lifetime. There are many indications of differences in sex ratio in many infectious diseases and in resistance to many varieties of trauma (20, 22). No consistent pattern emerges, although in general the female of the species is, as might be hoped, somewhat better geared for survival. However, tuberculosis has occurred more frequently among postpubertal women than among men of the same age. Infections of the urinary tract are more common in young women than in young men (8, 9). Attempts to reproduce these effects in the laboratory have not always met with success. The multitude of epidemiologic factors involved in the incidence of infection in a population and the effects of selection in a hospital environment are sufficiently great to make it uncertain to what degree the sex differences in resistance to infection reflect differences in biologic response to infectious agents rather than social, economic, and similar selection factors.

INFECTIONS OF THE URINARY TRACT DURING PREGNANCY

In another huge experiment of nature, pregnancy, hormonal changes beyond those that any experimenter would ordinarily envisage, occur regularly. Some observations have recently been made in relation to resistance to infection of the urinary tract during pregnancy and since these may have some relevance to the discussion, they are presented in some detail.

It has been amply confirmed by quantitative study of the bacterial flora of freshly voided urine that it is possible to detect a large reservoir of asymptomatic infections of the urinary tract (7–9, 17, 18). The finding of more than 100,000 bacteria (usually gram-negative rods) per milliliter of voided urine suggests with reasonable assurance that the individual from whom the specimen was obtained has asymptomatic but persistent bacteriuria, and a substantial, but as yet incompletely determined, likelihood of developing pyelonephritis (10, 15). Since pyelonephritis is the commonest complication of pregnancy and since late consequences of undetected renal infection such as hypertension and renal failure are more commonly found in women than in men, a detailed study of bacteriuria in pregnancy was undertaken.

The urines of more than 4000 women making their first prenatal visits to the outpatient department have been studied (10). The incidence of bacteriuria has been found to be in the range of 6 to 7 per cent from year to year. To document the predictive value of bacteriuria, a simple controlled therapeutic study was undertaken (table 2). Women who were less than 8 months pregnant, with bacteriuria documented on at least two separate occasions, were divided by alternation into two groups. Members of one group were treated to eliminate the bacteriuria and those in the other group were given a placebo. Extended clinical study of these patients showed

TABLE 2

Incidence of bacteriuria 3 to 12 months postpartum in patients with bacteriuria during pregnancy

Patient Group	Bacteriuria	
	Present	Absent
Untreated	15*	4
Treated	3	14

* Three of these patients developed acute pyelonephritis after 3 months' follow-up, were treated. and remained free of bacteriuria in the posttreatment cultures.

TABLE 3

Effect of treatment on occurrence of pyelonephritis in prenatal patients with asymptomatic bacteriuria

Patient Group	No. of Patients	No. with Pyelonephritis	Per Cent with Pyelonephritis
Control	48	20	42
Treated	43	0	0

TABLE 4

Occurrence of prematurity and infant death in bacteriuric pregnancy

Patient Group	Perinatal Deaths	Premature Infants
	%	%
Untreated bacteriuric	17	24
Treated bacteriuric	0	10
Nonbacteriuric	2	9

that about 40 per cent of pregnant women with bacteriuria were destined to develop pyelonephritis during pregnancy or during the immediate postpartum period. No woman whose bacteriuria was eliminated throughout pregnancy developed pyelonephritis of pregnancy and no woman who did not have bacteriuria at the time of initial screening of the urine developed pyelonephritis. Thus, pyelonephritis of pregnancy is apparently more or less completely preventable, and bacteriuria has predictive value in pregnancy. The untreated women have a high likelihood of retaining their bacteriuria for at least a year and probably longer after the termination of pregnancy (table 3).

When the fate of the infants that were born to the bacteriuric mothers was studied, it was found that there was an unusually high incidence of prematurity and of infant mortality in untreated bacteriuric mothers (table 4). The incidence of prematurity in untreated bacteriuric mothers is about 24 per cent. The incidence of perinatal death in the bacteriuric women is 17 per cent.

When patients were kept free of bacteriuria up to the time of delivery, there were no perinatal deaths in this small group, and the incidence of prematurity was only 10 per cent. The incidence of prematurity in 1000 consecutive nonbacteriuric mothers was 9 per cent. The difference in incidence of prematurity between the control and the treated patients has a p value of less than 0.01. If these data are borne out in continued studies now in progress, it may be possible to avoid 15 to 20 per cent of premature births and 20 to 25 per cent of perinatal deaths by detecting and treating bacteriuria during pregnancy.

How do these findings relate to hormonal mechanisms and resistance to infection? The answers are not clear but a few observations and speculations may be made. If the incidence of bacteriuria in pregnant women is plotted in relation to the duration of pregnancy at the time of the first prenatal visit, it becomes clear that most, if not all bacteriuria is acquired before the second month of pregnancy (figure 2). This was a wholly unexpected finding, since in most patients clinical illness develops during the latter half of pregnancy. It is obvious that bacteriuria appeared before the anatomical changes that are characteristic of pregnancy have had time to develop. Incidentally, a search for residual urine in the bladders of bacteriuric patients revealed no significant residual volume in these or in most nonbacteriuric women in comparable stages of pregnancy (10).

The evidence that pregnancy is implicated in the acquisition of bacteriuria is not yet very secure. Mrs. Mary Barnett has surveyed, in collaboration with our laboratory, about 200 female students in a nearby women's college. The incidence of bacteriuria was found to be 0.5 per cent. This is less than $\frac{1}{10}$ the incidence found in the pregnant women in our study, who, however, are in different economic and social brackets. It has been observed in a number of instances that treated women who remained free of bacteriuria for several months after delivery, upon return

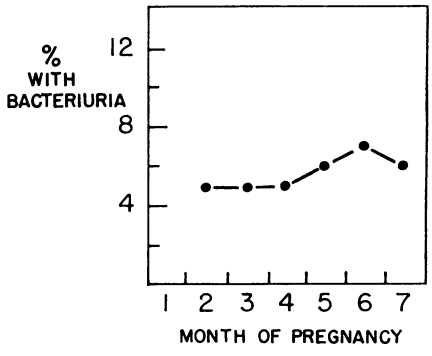

Figure 2. Incidence of bacteriuria in relation to duration of pregnancy at time of first prenatal visit.

to the prenatal clinic with a second pregnancy, once again were bacteriuric. Patients with infection who discontinue antibacterial treatment while pregnant, in the majority of instances become bacteriuric again by the time delivery occurs. On the other hand if treatment is maintained until delivery, less than one-fourth of patients have bacteriuria upon prolonged followup. All of these observations, although still not completely satisfactory, lead us to suggest that hormonal changes accompanying pregnancy are responsible for the persistence of bacteriuria in these patients.

What are the known hormonal changes in pregnancy, and how might they affect susceptibility to infection of the urinary tract? It is well established that the production of estrogen and progesterone increases slowly until the second trimester of pregnancy when the hormonal levels rise sharply (27). It can be argued that if these two hormones are responsible for the acquisition or maintenance of bacteriuria, its incidence should be expected to rise progressively during pregnancy. Our results demonstrate, however, that this does not occur. It seems equally unlikely that mechanical factors play much of a role, except perhaps in the precipitation of symptomatic disease. The mechanical changes in the urinary tract during pregnancy become progressively more severe after the first trimester, and yet the incidence of bacteriuria apparently does not increase.

During the first weeks of pregnancy striking increases occur in the production of chorionic gonadotrophin and corticosteroid (27). These two hormones, therefore, are being investigated with respect to their effects on the mucosa of the bladder and urethra. Whether a local metabolic effect or some other hormonally influenced basis exists for the inhibition of bacterial multiplication by the bladder, are problems for the future.

The data on prematurity are also of interest from the hormonal point of view. Autopsy studies of the dead babies and clinical observations of the mothers and babies offered no indication that active infection had spread from the urinary tract to precipitate premature labor. It has been known for many years, however, that the pregnant rabbit reacts to a single dose of endotoxin with the production of a generalized Shwartzman reaction, and that endotoxin often produces placental necrosis (1, 32). In collaboration with Drs. Vivaldi and Hajj, we have found that when pregnant rabbits are given endotoxin, sustained severe uterine contractions occur within less than 1 min. The nonpregnant uterus does not react to injections of endotoxin. In some manner, then, the hormonal changes of pregnancy appear to sensitize the uterus to rapid response to endotoxin. The significance of this sensitization remains to be investigated.

In summary, several salient points may be stressed. Better data are needed on phenomena of disease as they occur in nature as a guide to our experimental attack. No clear general statement concerning the influence of hormones on resistance to infection can be made at present. However, there is reason to believe from the studies of the influence of thyroid and adrenocortical hormones that means are at hand for a clear separation of the physiologic effects of an infection from the resistance mechanisms that deal with inhibition of bacterial multiplication in the host. Evidence has been presented to indicate that in some situations the toxic effect of an infection is so great that it may overshadow the capacity of the host to restrain the multiplication of infectious agents in host tissues. It has been stressed that the many factors that may influence the course of a disease such as diabetes mellitus must be separated from one another, otherwise it is difficult to determine whether the clinical expression of a disease represents on the one hand a disturbance of resistance mechanisms, or on the other, a disturbance of physiologic parameters that influence host response without influencing the rate of bacterial multiplication.

Some new information on pregnancy has indicated that bacteriuria has predictive value in detecting patients who are destined to develop pyelonephritis, and that it is associated with an increased incidence of prematurity and neonatal death. Evidence is presented which indicates that hormonal changes accompanying pregnancy act as predisposing factors in increasing the incidence of bacteriuria during pregnancy and in sensitizing the uterus to endotoxin.

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DISCUSSION

Administration of thyroxine can enable accelerated multiplication of human tubercle bacilli in rabbit lung after aerosol challenge with large numbers of organisms. In addition, thyroidectomy or hypothyroidism is associated with a reduction in antibody production, which can influence host resistance (Lurie, Philadelphia).

Estrogen administration to animals injected with tubercle bacilli does not seem to influence bacterial multiplication but may alter tissue permeability in such a way as to retard dispersion of microorganisms away from the site of inoculation and, therefore, to influence local suppuration. Corticotropin, on the other hand, may facilitate dispersion of bacteria and therefore have an apparent inhibitory influence on local suppuration (Lurie, Philadelphia).

Gram-positive bacteria are rarely found to be implicated in urinary tract infection, and what has been previously written about gram-positive cocci in the urine is confused by the failure to distinguish contaminants from those microorganisms producing infection (Kass, Boston).

Persistent or chronic urinary tract infection due to gram-negative bacilli might be expected to result in development of tolerance or resistance to the action of bacterial endotoxin. However, tolerance to the pyrogenic action of endotoxin has not yet been demonstrated in patients with such infection.