The clinical features, genetics, pathophysiology, and management of endocrine diseases in which primary hormone resistance is the fundamental defect have been reviewed. Primary hormone resistance has been documented for nearly all hormones—vasopressin, parathyroid hormone, growth hormone, adrenocorticotropin, thyrotropin, gonadotropins, insulin, androgens, cortisol, aldosterone, progesterone, thyroid hormones, and vitamin D. A striking exception is estradiol, a steroid that may be vital for early embryonic development. Most of the hormone unresponsiveness syndromes represent only partial defects, and it is likely that most such patients go unrecognized. Therefore, hormone resistance should be suspected not only when a patient presents with hypofunction of a particular endocrine system combined with high endogenous hormone levels but also whenever apparently normal function of an endocrine system is associated with inappropriately elevated levels of the corresponding hormone. The value of these defects in hormone responsiveness as a natural laboratory for the study of the normal mechanisms of hormone action is discussed.

Two types of endeavor dominated clinical endocrinology after its birth as a discipline in the mid 19th century. One involved the elucidation of clinical disorders that result from hormonal absence or deficiency. Such studies were followed by attempts to characterize and synthesize (or extract) the critical hormone and administer it to replace the deficit. The second involved identification and treatment of syndromes of hormone excess. These themes of hormone deficit and hormone excess advanced simultaneously with the development of methodologies for measurement of hormones in biologic fluids and for the study of the regulation of hormone synthesis, storage, and release in normal and pathologic states. Thus, for approximately 75 yr, clinical endocrinology developed without any significant insight into the mechanism of action of hormones within target tissues.

The field of endocrinology, basic and clinical, was ultimately changed by the description in 1942 of pseudohypoparathyroidism by Fuller Albright, Charles H. Burnett, Patricia G. Smith, and William Parson.1 This paper demonstrated the existence of a third type of endocrine disease in which the defect resides neither in hormone deficit nor hormone excess but in the capacity of the tissues to respond to the hormone—so-called hormone resistance. The authors hypothesized that pseudohypoparathyroidism is due to a deficiency in or interference with some hypothetical substance with which parathyroid hormone reacts. They drew an analogy between the syndrome and the Seabright-Bantam rooster in which female feathering is believed to be due to resistance to the action of the male hormone and suggested that other types of hormone resistance must exist in clinical medicine. In subsequent studies Albright and his colleagues recognized the hereditary nature and variability in the disorder.2,3 The suggestion was made that resistance to hormone action be termed a "Seabright-Bantam syndrome."

The concept that an endocrinopathy could result because the tissues cannot respond to normal or increased levels of a hormone has had far-reaching implications for endocrinology. First, more and more forms of hormone resistance have been identified so that by now syndromes have been described in which disease results from resistance to any of several hormones.5,6 Second, the concept of hormone resistance has served as a major stimulus for the study of how hormones act within cells. Although pseudohypoparathyroidism was described before the existence of hormone receptors was recognized, the concept that there is a chemical reaction between the hormone and a portion of the cell had its inception in the origi-
nal Albright paper. Each patient with hormone resistance is a natural laboratory for investigating the mechanism of hormone action, and study of such patients has resulted in two significant advances in clinical science: identification of many specific steps in hormone action and recognition of the remarkable heterogeneity of endocrine disorders. Third, abnormalities of receptors are now implicated in the pathogenesis of diseases outside the endocrine domain, such as myasthenia gravis and familial hypercholesterolemia. Finally, description of various syndromes of hormone resistance and identification of the biochemical pathophysiology of the underlying defects has had important therapeutic implications. To design a rational therapy, it is necessary to know the exact site in cellular metabolism at which the disorder occurs.

The presence of hormone resistance does not necessarily imply an abnormality at the level of the target cell. A variety of pathophysiologic mechanisms known to cause hormone resistance (apparent or real) are summarized in Table 1. For example, resistance to endogenous hormones only can result from the formation of incomplete or abnormal hormones such as the elevated plasma thyrotropin in certain forms of hypothalamic hypopituitarism, the abnormal parathyroid hormone in the syndrome of pseudohypoparathyroidism, and the elevated immunoreactive insulin in subjects with familial hyperproinsulinemia. Subjects with such disorders respond in a normal fashion to the administration of normal hormones.

Individuals with true hormone resistance, in contrast, are insensitive to both endogenous and exogenous hormones; such resistance can arise from a variety of causes (Table 1). These include (1) physiologic antagonism as in the insulin resistance of acromegaly; (2) development of antibodies that inactivate or block the active hormones such as antibodies to insulin in insulin-treated diabetics and antibodies to thyroid hormones in certain subjects; (3) development of antibodies to hormone receptors as in certain forms of diabetes mellitus; (4) absence of target cells as in Leydig cell agenesis; (5) primary abnormalities of the hormone receptor either at the cell surface as in vasopressin-resistant diabetes insipidus or in the cytosol as in testicular feminization, and (6) disorders of the post-receptor effector mechanisms within target cells as in certain forms of hereditary male pseudohermaphroditism.

In addition to the primary syndromes, some forms of hormone resistance are secondary to other physiologic derangements. For example, the angiotensin resistance in the Bartter syndrome is secondary and remote to the underlying principal defect. Thus, the subject of hormone resistance has become complex.

This review is focused on the syndromes in which resistance to hormone action is believed to be primary to the pathogenesis of the disorder. We have further limited discussion to those disorders in which the defect is thought to reside at the level of the target cell, either in the receptors themselves or in the post-receptor effector mechanisms within cells. Exceptions have been made when discussion of other types of defects is essential for the consideration of pathophysiology and differential diagnosis. These disorders have been subdivided arbitrarily into those involving hormones in which the primary receptor mechanism is on the cell surface, and those involving hormones in which the receptor is intracellular because the mechanisms of action are fundamentally different.

### HORMONES WITH CELL SURFACE RECEPTORS

The hormones in the first class bind to surface receptors localized on the cell membrane (Fig. 1). The activity of such hormones is believed to be mediated largely, if not entirely, by so-called second messengers, produced by the cell membranes. This mechanism applies to some protein hormones and to the biogenic amines. In most instances, the second messenger is cyclic adenosine 3',5'-monophosphate (cAMP). Calcium and other nucleotides such as cyclic...
guanosine 3',5' monophosphate (cGMP) may act as second messengers for some hormones. The cellular concentration of cAMP is controlled by two enzymes with opposite activities. Adenylate cyclase (Ac), localized in the plasma membrane converts adenosine triphosphate (ATP) into cAMP. Phosphodiesterase, mainly localized in the cytosol, inactivates cAMP by converting it to 5'-adenosine monophosphate (5'-AMP). Hormones that act at the cell surface (H) interact with this system to stimulate the production of cAMP. They form a reversible complex with specialized membrane proteins. These proteins are specific for a particular hormone, bind the hormone with high affinity but limited capacity, and are commonly called "receptors" (R). The formation of the hormone-receptor complex is coupled to a stimulation of the adenylate cyclase. The biochemical mechanisms that underlie this transduction mechanism are poorly understood, but recent evidence indicates that GTP may play an important role in this process. The means by which cAMP mediates the spectrum of hormone effects also remain elusive. Phosphorylating enzymes, known as protein kinases, undoubtedly play an important role in this process. These enzymes are composed of catalytic (C) and regulatory (R*) subunits. Binding of cAMP to the regulatory subunit frees the catalytic subunit and leads to activation or inactivation of various enzymes by phosphorylation. In instances where calcium serves as the second messenger, the mechanism by which it acts to mediate hormonal effects is also unclear. Another type of hormone, i.e., insulin, clearly binds to receptors on the cell membrane, but the mechanism by which this binding is translated into physiologic effects is unknown.

It is evident from the simplified scheme in Fig. 1 that a variety of possibilities exist for defects resulting in hormone unresponsiveness. These include (1) impaired formation of the hormone-receptor complex; (2) defective transduction system so that the formation of the hormone-receptor complex does not result in effective stimulation of the adenylate cyclase; (3) defective adenylate cyclase, or (4) overactive phosphodiesterase. Further defects may be situated in (5) the protein kinase; (6) the enzymes or proteins that are substrates for this kinase; (7) the phosphatases that antagonize protein kinase, and (8) biochemical reactions that mediate hormonal effects independent of cAMP.

At each of these different steps, interactions of ligands with binding proteins or interactions of substrates and enzymes are involved. Defects may result when the concentration of one of these binding proteins (receptor, regulatory subunit of the protein kinase, etc.) or enzymes (adenylate cyclase, catalytic subunit of the protein kinase, etc.) is lowered, or when the affinity for the ligand or substrate is changed. In the simplest situation, where there is a direct relationship between the binding reaction or enzymatic step studied and the final hormone response, such changes in concentration or affinity result in changes of the dose-response curve for the hormone as illustrated in Fig. 2. If the defect is in the amount of binding protein or enzyme, the maximum response that can be obtained at saturating levels of the hormone is decreased whereas the concentration of hormone at which a half-maximal response is obtained will be unchanged (Fig. 2, Situation 1). If the defect is in the affinity of the ligand for the receptor or enzyme, the maximum response is not impaired, but the hormone concentration needed to reach this response will be increased (Fig. 2, Situation 2). Examples of both situations will be illustrated further in this review.
Fig. 2. Theoretical dose-response curves in hormone resistance. The normal dose response curve is shown by the solid line. In one type of possible abnormality (1), maximal response is deficient at all concentrations (C) of the hormone, but the amount required for half-maximum activity is normal. In the other possibility (2), maximal response is normal at supraphysiological concentrations of the hormone. C' and C* are the concentrations of hormone required for half-maximal responses in the two situations.

Antidiuretic Hormone (Vasopressin)

The form of resistance to a hormone that acts at the cell surface that has been worked out in most detail from a pathophysiologic and biochemical point of view is nephrogenic or vasopressin-resistant diabetes insipidus.\textsuperscript{28-30} This is in part due to the fact that an animal model for this disease has been identified. The disorder has been the subject of several extensive reviews.\textsuperscript{31-33}

Clinical features. Antidiuretic hormone (ADH) or vasopressin enhances the permeability to water in the cells of the collecting duct of the kidney. Because there is a steep osmotic gradient from tubular lumen to the renal medullary interstitium, this enhanced permeability results in a movement of water from the tubular lumen to the interstitium, and consequently the production of concentrated urine. Nephrogenic diabetes insipidus is characterized by unresponsiveness of the tubular cells lining the collecting ducts to ADH. Polyuria, permanent production of dilute urine, and compensatory polydipsia are the clinical hallmarks. If the syndrome is not recognized, or if water intake is inadequate, dehydration and death result. In infants, the persistent polyuria and polydipsia can be so severe as to cause chronic dehydration and hypernatremia and result in physical and mental retardation.

Available data indicate that the disorder is transmitted by an X-linked mode of inheritance. Male patients commonly display complete unresponsiveness whereas variable expressivity of the gene frequently occurs in females.\textsuperscript{31} A significant number of patients in North America may be descendants of immigrants that arrived in Nova Scotia in 1761 on the ship Hopewell.\textsuperscript{34} The disease has also been described in a black kindred in North America where racial admixture with the previous patients could not be excluded,\textsuperscript{35} in an Australian aboriginal kindred,\textsuperscript{36} in several European kindreds,\textsuperscript{37} and in sporadic forms.

Pathophysiology. Nephrogenic diabetes insipidus represents a defect in the interaction of ADH with its target cells. The urine osmolality of these patients is not affected by large doses of ADH.\textsuperscript{28-30} Recent measurements of plasma arginine vasopressin by radioimmunoassay have demonstrated a classical hyperbolic dose-response relationship between the hormone levels in different states of hydration and urine osmolality both in normal controls and in patients with pituitary diabetes insipidus; in patients with nephrogenic diabetes insipidus a similar relationship of vasopressin concentration to fluctuating states of hydration is noted, but there is no accompanying alteration in urine osmolality.\textsuperscript{37,38} The ADH secreted by these patients has been shown to be biologically active, for example, if injected into hydrated rats,\textsuperscript{39-42} and there is no evidence for an increased rate of inactivation of the hormone.\textsuperscript{43} The osmotic gradient in the interstitium is not affected primarily.\textsuperscript{44}

The interaction of ADH with its target cells proceeds essentially as outlined in Fig. 1 for a second messenger-mediated system. The epithelial cells lining the collecting ducts are highly polarized. Vasopressin receptors are localized on the basal and lateral cell membranes whereas the change in water permeability takes place in the membrane lining the tubular lumen.\textsuperscript{45} In plasma membrane preparations derived from pig kidney medulla, a close correlation has been demonstrated between the amount of radioactive vasopressin bound to plasma membranes and the activation of adenylate cyclase.\textsuperscript{46} The manner in which cAMP increases tubular permeability to water remains enigmatic. cAMP-dependent pro-
tein kinases, the activity of which can be increased in vivo by ADH, have been demonstrated in kidney cytosol. Moreover, proteins that can be phosphorylated by these protein kinases have been shown to be present in the cell membranes lining the tubular lumen. It is conceivable that these proteins control the diameter of the pores in the cell membrane. Integrity of the microtubular microfilamentous system underneath the cell wall is essential for a normal renal response to ADH, and ordered aggregation of the intramembranous particles in the toad bladder, another vasopressin target organ, has been demonstrated to correlate with vasopressin induced osmotic water flow.

Study of the subcellular mechanisms underlying a disorder such as nephrogenic diabetes insipidus is difficult in humans. The existence of strains of mice with a similar disease (although with a different genetic mechanism) has provided an exceptional opportunity for a pathophysiologic and biochemical approach to this syndrome. A strain that has proven particularly valuable is the one studied by Dousa and Valtin in which severe diabetes insipidus is inherited as a polygenic trait. When normal controls of this strain are given free access to water and food, they concentrate urine to 2800 milliosmols/kg water. Mutants with severe diabetes insipidus have an extreme abnormality in the concentration of urine. Each day they excrete a volume of hypotonic urine equal to about 150% of their body weight, and they lack the ability to respond to ADH with an increase in urine osmolality. The concentrating defect is not secondary to a reduction of the corticopapillary interstitial osmotic gradient. Studies of the influence of ADH on the activity of adenylate cyclase in cell-membrane preparations derived from the renal medulla of these animals provide insight into the mechanisms underlying this hormone resistance. Basal adenylate cyclase activity (in the absence of ADH) is equal in the control and severe diabetes insipidus strains. Striking differences are observed, however, in the amount of cAMP produced by saturating concentrations of ADH. At saturation, the activity of the adenylate cyclase is about 40% lower in the mutant mice than in controls. Nonspecific stimulation of the adenylate cyclase by sodium fluoride results in equal activities in normal and affected animals, suggesting that the defect does not reside in the enzyme itself but in the formation of the hormone-receptor complex or in the activation of the adenylate cyclase by this complex. It is important to note that only the maximum level of adenylate cyclase activity is affected and that the concentration of hormone needed to get half-maximal stimulation is comparable in mutant and normal mice (Fig. 2).

A reasonable explanation for this defect is that a receptor with normal kinetic characteristics is present but that the concentration of this receptor is lower in affected mice. The defect has been shown to be limited to vasopressin. Stimulation by parathyroid hormone of the adenylate cyclase derived from the renal cortex is the same in normal and affected animals. Moreover, no significant differences have been demonstrated in the known steps beyond the adenylate cyclase, namely phosphodiesterase, the protein kinase, or the microtubular, microfilamentous system. One of the remaining questions is whether a 40% lowering of maximal adenylate cyclase activity can explain a tenfold decrease in urine osmolality. Computer simulation of the renal countercurrent system suggests that this is possible.

Data in the human are not as clear-cut as in the mouse. Defective renal retention of radioactive vasopressin (presumably reflecting diminished receptor binding) has been demonstrated with the use of a noninvasive external counting procedure in a patient with nephrogenic diabetes insipidus. On the other hand, data concerning renal cAMP production in human nephrogenic diabetes insipidus are contradictory. One of the problems is that even in normal persons or patients with pituitary diabetes insipidus, the increase of urinary cAMP excretion after stimulation with ADH is small, considering normal physiologic variations in cAMP output. A defect in urinary cAMP excretion in patients with nephrogenic diabetes insipidus treated with ADH has been reported by Fichman and Brookner, by Bell et al., and by Hogg and Balfe. In contrast, Monn et al. observed normal urinary cAMP in six children with nephrogenic diabetes insipidus given ADH. These heterogeneous clinical findings suggest that human nephrogenic diabetes insipidus, like several other unresponsiveness syndromes, probably constitutes a heterogeneous disorder. Some
patients may have a defect in the receptor binding of ADH or the activation of adenylate cyclase by the hormone-receptor complex. Others may have a defect distal to the formation of cAMP.57-60

In addition to genetic forms of nephrogenic diabetes insipidus, there are several secondary forms. Vasopressin resistance has been observed in association with a variety of renal tubular lesions, in hypokalemia and hypercalcemia, during methoxyflurane anesthesia and demeclocycline therapy, during the use of some vasopressin analogs, and after the administration of lithium salts.19,61 Although a detailed discussion of these conditions is beyond the scope of this review some of them may be of relevance in view of the resemblance of the underlying biochemical mechanisms to the disturbances observed in the hereditary form of the disease. For example, hypercalcemia has been shown to block the increase in excretion of cAMP after the administration of ADH62 whereas lithium blocks maximal cAMP generation in a dose-dependent way without affecting the dose necessary for a half-maximal response.63 It also interferes with steps beyond the production of cAMP.64

Parathyroid Hormone

Clinical features. The clinical features of pseudohypoparathyroidism were described in considerable detail in the original papers by Albright and his colleagues:1-3 (1) clinical characteristics of hypoparathyroidism including enhanced neuromuscular excitability, hypocalcemia, and hyperphosphatemia; (2) resistance to the action of parathyroid extract in regard to both phosphate excretion and a rise in serum calcium; (3) correction of the disorder by large doses of dihydrotestosterone; (4) a syndrome characterized by short stature, obesity, round faces, shortening of metacarpal and metatarsal bones, ectopic calcification, cataracts, and mental retardation (so-called Albright's hereditary osteodystrophy); (5) familial occurrence, and (6) the presence of normal (or increased) activity of the parathyroid glands. The authors also recognized that the skeletal abnormalities could exist in the absence of hypocalcemia or documentable resistance to parathyroid hormone and called this variant form of the disorder pseudopseudohypoparathyroidism.3

In subsequent years, many additional patients have been described with these typical features.55-68 Convincing genetic data have been assembled to indicate that pseudohypoparathyroidism and pseudopseudohypoparathyroidism are variable expressions of the same mutant gene that can be manifested in different ways in members of the same family.69,70 Interestingly, the same individual may have varying manifestations of either pseudohypoparathyroidism or pseudopseudohypoparathyroidism at different times in life.71

It is not clear whether the disorder is inherited as an X-linked dominant or as an autosomal dominant that is manifested more commonly in women.69 At least one pedigree has been reported in which male to male transmission of the disorder appears to have occurred,72 suggesting that in some families it results from an autosomal mutation.

In recent years, a number of additional variants have been described. These include patients with parathyroid hormone resistance, hypocalcemia, and hyperphosphatemia but no hereditary osteodystrophy;73 patients with resistance to the renal and intestinal actions of the hormone but not to the skeletal effects, so that they have coexisting hypocalcemia and osteitis fibrosa of the bones (so called pseudohypophyperparathyroidism);74-76 and patients with the complete picture of pseudohypoparathyroidism except for normal serum calcium.77 At the present there is considerable confusion regarding these various syndromes. It is not known whether they represent variable expressions of the same mutant gene or whether they are (at least in part) separate mutations. No adequate pedigree analyses have been reported that would allow one to resolve this issue, and in most instances these latter variants appear to be sporadic.

In the recent past, a series of other endocrinopathies have been noted with increased frequency in pseudohypoparathyroidism.78 Hypothyroidism with selected deficiency of thyrotropin has been documented in some patients79 whereas other subjects have elevated levels of thyrotropin and apparent unresponsiveness to the latter hormone.80,81 A high incidence of defective prolactin secretion has also been reported in a recent series of patients.82 Menstrual irregularities, delayed puberty,
amenorrhea, and infertility have been present in several case reports, and hypoestrogenism with elevated gonadotropins indicative of gonadotropin resistance of the ovaries and resistance to the action of glucagon have recently been reported in a 17-yr-old woman with pseudohypoparathyroidism. The potential importance of these associated endocrinopathies to understanding the basic defect will be discussed later.

Pathophysiology. The biologic actions of parathyroid hormone (PTH) and the major processes that are known to alter these actions can be summarized as follows: The three major target tissues for PTH are kidney, bone, and intestine. In the kidney, the major effects are stimulation of phosphate excretion, enhancement of calcium reabsorption, and formation of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D. In bone, PTH action has been divided into two functions, calcium replacement and bone remodeling. The former is believed to be mediated by osteocytes and plays an important role in the control of plasma calcium concentration. The latter action is apparently mediated by osteoclasts. In the intestine, PTH augments calcium absorption. These different activities of PTH are closely interrelated. The absorption of calcium in the intestine, for instance, is entirely dependent on the formation of 1,25-dihydroxycholecalciferol in the kidney. PTH activity in bone is at least partly dependent on this active form of vitamin D as well as on the plasma concentration of calcium and phosphate. Conversely, increases in plasma calcium secondary to PTH action in the bone enhance the activity of PTH in promoting phosphate clearance by the kidney, and increases in plasma phosphorus in response to PTH action in bone inhibit 1,25 dihydroxycholecalciferol formation.

Thus, the actions of parathyroid hormone on bone, kidney, and intestine depend in large part on an interlocking system involving (at a minimum) the hormone and its receptor-effector system, active forms of vitamin D, and plasma calcium and phosphorus. The balance of these parameters may vary at different times of life and under differing dietary and environmental conditions so that resistance to the hormone may express itself differently in different individuals and in the same individual at different times in life.

As mentioned in the introduction, many factors can interfere with the activity of a hormone before it reaches its target tissues. Most of these factors have been excluded as an explanation for the hormone resistance in pseudohypoparathyroidism. A patient who secreted an immunologically cross-reacting, but biologically ineffective, form of PTH has been described; the name pseudoidiopathic hypoparathyroidism has been proposed for this entity. It is highly improbable, however, that such a defective hormone accounts for the unresponsiveness to PTH of patients with pseudohypoparathyroidism since they respond normally when given exogenous PTH. Defective peripheral conversion of secreted PTH to its more active fragment seems equally unlikely as an explanation since synthetic bovine and human PTH fragments containing amino-acids 1–34 are also ineffective in these patients. Antibodies directed against PTH have been demonstrated after repeated injections of the hormone, and such antibodies may result in acquired resistance to PTH.

Although it has been suggested that an autoimmune process might underlie the multihormonal defects in some patients with pseudohypoparathyroidism, no evidence for the presence of PTH-directed antibodies has ever been obtained in untreated patients. Increased concentrations of calcitonin have been found in the thyroid gland of patients with pseudohypoparathyroidism.
hypothesis that PTH activity in the kidney is mediated by cAMP is supported by three types of data. (1) Within minutes after the administration of PTH to normal persons, CAMP excretion in urine increases ten- to seventyfold. A similar response is observed after addition of PTH to kidney tissue in vitro. (2) Administration of dibutyryl CAMP in vivo reproduces the effects of PTH on calcium and phosphorus excretion by the kidney. (3) Inhibitors of phosphodiesterase such as theophylline enhance PTH effects, whereas stimulators of the same enzyme result in diminished activity. A similar increase in CAMP production has been demonstrated after addition of PTH to bone cells in vitro. Little is known, however, concerning the steps beyond the formation of CAMP. As mentioned above, calcium, phosphorus, and 1,25-dihydroxycholecalciferol all may act as permissive factors or even as second messengers of PTH action in at least some target cells.

The demonstration by Chase et al. that PTH increases the urinary excretion of CAMP in normal controls and in patients with hypoparathyroidism and pseudopseudohypoparathyroidism, but that this response is absent or markedly blunted in patients with pseudohypoparathyroidism, suggests that defective CAMP generation is involved in the pathogenesis of pseudohypoparathyroidism. However, this hypothesis was challenged by the subsequent observation that the PTH-sensitive adenylate cyclase in the kidney of a patient with pseudohypoparathyroidism responded in vitro with a log-linear dose response to increasing doses of PTH whereas such a response was not observed in vivo. This apparent discrepancy between in vivo and in vitro data may be clarified by a recent report by Drezner and Burch. These authors also observed that the adenylate cyclase in renal tissue derived from a patient with pseu-

dohypoparathyroidism responded normally to PTH added in vitro at saturating concentrations of ATP. However, the adenylate cyclase of the patient had a threefold lower affinity for ATP, and the response to PTH was markedly impaired at subsaturating concentrations of ATP. If these data can be confirmed, the basic defect in PTH action in pseudohypoparathyroidism may be a lowered affinity of the PTH-responsive, adenylate cyclase of the renal cortex for its substrate ATP. Accordingly, this would represent a defect at level 3 in Fig. 1. As mentioned above, several patients with pseudohypoparathyroidism have presented evidence of resistance to thyrotropin, gonadotropins, and glucagon. Although no extensive genetic studies of these various defects have been published, the possibility should be considered that a more generalized defect of the adenylate cyclase exists in some patients.

A major unresolved issue is whether the many variants of pseudohypoparathyroidism represent variable manifestations of a single underlying defect or different mutations. These variants have been defined both on the basis of functional studies and clinical criteria. For example, a form of pseudohypoparathyroidism has recently been described with a typical clinical presentation and characterized by absence of phosphaturic and hypercalcemic responses to PTH, but a normal increase in urinary CAMP in response to the hormone. As noted in Table 2, this disease entity has been called pseudohypoparathyroidism Type II to distinguish it from the vast majority of cases (pseudohypoparathyroidism Type I) in which the renal CAMP response to PTH is absent. Only a few patients with this form of the disease have been described, and all cases to date appear to be sporadic. It has been proposed that the Type-II disorder may represent a defect in the reception of the CAMP signal. However, there are no
studies available on the effect of dibutyryl cAMP in these patients. An alternative hypothesis might be that the disorder represents variable manifestation of the Type-I defect in which the PTH responsive cells of the kidney are not as severely affected. In fact, the mean phosphorus level in Type-II patients is low compared to the majority of patients with pseudohypoparathyroidism, and in one patient a normal phosphaturic response of the kidney was restored after calcium administration. 

Whatever the basic defect in the PTH unresponsiveness, there is ample clinical evidence that the resistance is variably manifested in different target tissues. The most constantly and profoundly affected organ in pseudohypoparathyroidism is the kidney. This may be due at least in part to the fact that the present clinical screening techniques for the syndrome rely heavily on demonstration of a low or absent cAMP response in the urine following PTH administration. Renal responses to PTH have recently been compared in normal controls and a variety of patients with pseudohypoparathyroidism by Moses, Breslau, and Coulson. The most commonly observed disturbance, apart from the impaired response in cAMP excretion, was failure to decrease the ratio of calcium to sodium clearance. Other responses, however, such as the excretion of calcium, sodium, potassium, phosphate, and bicarbonate were low in some patients but approached normal in others.

In the vast majority of the patients with pseudohypoparathyroidism, the osseous response to PTH is apparently only partially impaired. Only moderate degrees of bone thickening are observed as compared to patients with hypoparathyroidism, and several instances of osteitis fibrosa have been documented. Urinary hydroxyproline is normal or slightly elevated, while bone turnover in pseudohypoparathyroidism varies from low normal to markedly increased levels. At least part of the poor response of the osseous system to PTH is due to impaired formation of 1,25-dihydroxycholecalciferol in the kidney. Diminished responsiveness because of prolonged exposure to high levels of PTH may be another pathogenic factor.

Since the effects of PTH on intestinal calcium absorption are believed to be mediated by 1,25-dihydroxycholecalciferol, and since PTH in the kidney regulates the formation of this metabolite, a defective uptake of calcium by the gut can be accounted for by the low levels of this active vitamin-D derivative secondary to the unresponsiveness of the kidney to PTH. The ability of 1,25-dihydroxycholecalciferol to restore calcium uptake by gut is in keeping with this hypothesis.

In addition to the various physiologic and dietary factors that may influence the action of parathyroid hormone in different tissues, McKusick has pointed out that if pseudohypoparathyroidism is in fact X-linked, a considerable portion of the variable manifestations of the disorder could be explained by the Lyon hypothesis; namely, random inactivation early in embryogenesis of one X-chromosome in 46,XX heterozygotes for the disorder could result in different tissues with normal or deficient receptor mechanisms in different individuals.

For these various reasons, it is not possible to know whether the variants of pseudohypoparathyroidism represent variable manifestations of the same mutant gene responsible for the common disorder. Therefore, the nosologic classification of patients with PTH unresponsiveness shown in Table 2 must be viewed as tentative. The Type-I disorder is distinguished by an absent response of urinary cAMP to PTH administration (in severely affected patients), the presence of abnormalities in calcium metabolism suggestive of hypoparathyroidism, and the presence or absence of clinical stigmata of hereditary osteodystrophy. Until more data have been accumulated on the normal mode of action of PTH and on the disturbance of this system in pseudohypoparathyroidism Type 1, this class of patients can best be regarded as a population having an X-linked or autosomal dominant mutation with a variable degree of expressivity. The degree of expressivity determines the organs in which PTH unresponsiveness is manifest and the degree of impairment in these organs. As a rule, the kidney is affected most profoundly, and the majority of the defects in the other target tissues can be accounted for by low plasma levels of 1,25-dihydroxycholecalciferol, low plasma calcium, and high plasma phosphorus. The presence or absence of hereditary osteodystrophy is also probably the consequence of variable disturbances in PTH responsiveness and calcium
metabolism. No firm data are available on this subject. Pseudohypoparathyroidism, commonly diagnosed by clinical signs of hereditary osteodystrophy, represents the mildest expression of pseudohypoparathyroidism as indicated by the high incidence of this entity in family members of Type-I patients. Many minimally affected patients may go undiagnosed.

Pseudohypoparathyroidism Type II is diagnosed on the basis of clinical signs of hypoparathyroidism, normal renal response to PTH with respect to cAMP excretion, but absent response with respect to phosphate excretion in the untreated state. Hereditary osteodystrophy may be present or absent. Only a few cases have been described, all of which are sporadic. It is not clear whether this entity represents a completely different mutation than the Type-I disease or a variant of this disease in which the defect is localized mainly or only in the bone.

Growth Hormone

Clinical features. At least two forms of unresponsiveness to human growth hormone (hGH) have been described (Table 3).105,106 The first involves the pygmies of the tropical rain forest in Africa. The male Babinga pygmy has an average height of 145 cm, and the height of the female averages 139 cm. They are normally proportioned dwarfs with normal sexual development, and the phenotype resembles that of patients with isolated hGH deficiency except for the absence of the typical doll-like facies, wrinkled skin, and truncal obesity. Normal plasma growth hormone was documented by Rimoin et al.107 The phenotype of the African pygmy represents one extreme of the normal variation in stature that exists among ethnic groups. No data are available on the inheritance of this trait, but it is probably polygenic. Pygmy Bantu hybrids are intermediate in size between the two parental types.108

The second form of unresponsiveness to hGH is the Laron dwarf. On clinical examination, the Laron phenotype cannot be distinguished from that of patients with monotropic deficiency of hGH. Affected individuals have normal weight and length at birth but grow slowly (below the third percentile) and develop the typical features of normal infantile body proportions, small face and mandible, truncal obesity, high pitched voice, and deep temporal recession of the hairline. In contrast to dwarfs with isolated hGH deficiency, however, the plasma levels of the hormone tend to be high, even up to the acromegalic range.109-110

Approximately 40 Laron dwarfs have been identified.110 Although this syndrome is most frequently observed in Oriental Jews, patients have been described throughout the world. Since a high frequency of consanguinity has been observed (17 patients belonging to 5 families), an autosomal recessive inheritance is suggested.110,111

Pathophysiology. It is presently accepted that an important part of the activity of growth hormone and particularly its effect on the skeletal system is mediated by somatomedins. Somatomedins are mainly secreted by hepatocytes, and their secretion is stimulated by the interaction of growth hormone with receptors on the surface of these cells.112 Other actions of growth hormone, for instance, its lipolytic effect in adipocytes113 and its insulinotropic effect on pancreatic beta cells,114 appear to be independent of somatomedin.

The African pygmies share several metabolic features with patients having the classical form

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<tr>
<th>Disorder</th>
<th>Inheritance</th>
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<th>Somatomedin</th>
<th>Response to Administration of Human Growth Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated deficiency of human growth hormone, Type I</td>
<td>Autosomal recessive</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Laron dwarfs</td>
<td>Autosomal recessive</td>
<td>Increased</td>
<td>Further</td>
<td>Low</td>
</tr>
<tr>
<td>African pygmy</td>
<td>Possibly polygenic</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Modified from Rimoin and Solomon 108

![Table 3. Comparison of Growth Hormone Deficiency and Resistance](attachment:image_filename)
of isolated hGH deficiency (hGH deficiency type I). Even when pretreated with a high protein, high carbohydrate diet (to correct any coexisting dietary deficiencies) the pygmies are insulinopenic and hypersensitive to the effects of exogenous insulin. Growth hormone levels are normal, as mentioned, and somatomedin concentrations are within the normal range. Growth hormone response to stimulation by hypoglycemia and arginine administration is appropriate. However, the administration of exogenous growth hormone, although accompanied by an appropriate rise in somatomedin, results in no lipolytic, insulinotropic, or nitrogen-retaining effect in the pygmy. At present, the growth hormone resistance can best be explained by an unresponsiveness of the peripheral tissues to the actions of somatomedin. An unresolved question is why the effects of growth hormone that are supposedly mediated by a direct interaction on the target cells (e.g., the lipolytic effect) are also impaired. It might be postulated that either somatomedin or somatomedin-like substance in fact plays a role in these effects; alternatively, the defect may be of a more general nature than simply a disturbance in somatomedin-target cell interaction. An autosomal recessive mutant of the mouse known as the pygmy (pg) has been described. These mice are also unresponsive to growth hormone and may prove to be a model for the study of the human pygmy.

Laron dwarfs tend to have high rather than normal basal levels of immunoreactive growth hormone. Hormone secretion in response to hypoglycemia, arginine infusion, and the administration of dihydrosomatostatin is normal. They respond poorly to the administration of growth hormone, and in contrast to pygmies, the somatomedin levels are low. Plasma somatomedin concentration does not increase after growth hormone stimulation. Two hypotheses have been proposed to explain this syndrome. Laron et al. originally suggested that the growth hormone secreted by these patients might be biologically inactive and even block the growth hormone receptor making these patients resistant to the action of exogenous hormone. However, all evidence accumulated to date indicates that the growth hormone secreted by these patients does not differ physically, immunologically, or biologically from normal. No antibodies against growth hormone have been demonstrated in the serum of these patients, and the immunologic behavior of the growth hormone from plasma of Laron dwarfs is normal when studied with a variety of antibodies. The circulating growth hormone has its expected intrinsic prolactin activity when tested in vitro in mouse mammary-gland cultures and it behaves exactly as the growth hormone from normal subjects with a radioreceptor assay. Accordingly, the second hypothesis—a generalized defect of the growth hormone receptors, resulting in absence or marked blunting of both the production of somatomedin and the direct effects of growth hormone—appears to be the most plausible explanation at the present time. The defect may be only partial, however, since both enhanced growth and potentiation of peak plasma insulin levels in response to glucose administration have been observed after long-term treatment with human growth hormone.

Thyrotropin

Only one case of thyrotropin unresponsiveness has been described. This report describes a boy with congenital hypothyroidism, physical findings of cretinism, low levels of thyroid hormones, and high circulating thyrotropin. No evidence was obtained for any associated endocrine disorder. The parents of the proband were first cousins once removed and were free of thyroid disease, findings suggestive of autosomal recessive inheritance. The findings included low peripheral levels of thyroid hormones, a normal radioactive iodine uptake, absence of mitoses in a thyroid biopsy, and absence of thyroglobulin in the thyroid gland. There was no response to the administration of exogenous thyrotropin in vivo, and addition of thyrotropin to tissue slices in vitro did not change the metabolism of C-glucose. Alternative explanations such as metabolic blocks that result in deficient thyroid synthesis (e.g., iodine transport defect, peroxidase defect, dehalogenase defect, or coupling defect) were excluded on clinical and biochemical grounds.

The biochemical basis for the thyrotropin unresponsiveness in this patient is unclear. Since the activity of circulating thyrotropin in the
The patient was about four times normal in a bioassay, the presence of a biologically less active form of thyrotropin, as has recently been postulated by Illig et al., seems unlikely. The presence of interfering antibodies directed against thyrotropin can be excluded on the same basis. Thyrotropin-binding inhibitor immunoglobulins have been documented in Graves' disease and Hashimoto's thyroiditis, but it seems unlikely that such proteins would be present congenitally, and no antibodies directed against cytoplasmic or colloid antigens could be detected in the patient by immunofluorescence techniques. It has recently been demonstrated that high amounts of thyroglobulin can interfere with thyrotropin binding at the level of its receptor sites. This protein was absent, however, in the patient described. Accordingly, on the basis of the available data, a defect in either the thyrotropin receptor or in post-receptor mechanisms mediating thyrotropin activity at the level of its target cells remains the most likely explanation for the observed defect.

Adrenocorticotropic Hormone

Clinical features. Although earlier patients with the disorder had been described, unresponsiveness to adrenocorticotropic hormone (ACTH) was first delineated as a distinct clinical and pathophysiological entity by Migeon et al. in 1968. The syndrome is characterized by absent or markedly impaired production of cortisol in the presence of high circulating levels of ACTH, normal production of aldosterone, and normal sodium balance. There is no increased production of cortisol precursors (as in congenital adrenal hyperplasia), and no increase in plasma cortisol, urinary 17-hydroxysteroids, or urinary 17 ketosteroids in response to exogenous ACTH. Typically, patients present early in life with feeding problems (chronic spitting, vomiting, failure to thrive), hyperpigmentation, lethargy, hypoglycemia, and convulsions. If undiagnosed or untreated, shock and death occur in early childhood.

Until 1972, approximately 20 patients had been described in 16 families. In nearly all the families, however, there are reports of other sibs who died in the perinatal period or in early childhood with clinical symptoms suggesting that they were affected by the same disease. The first six patients reported (out of five families) all happened to be males and the possibility of an X-linked recessive mode of inheritance was suggested. No such male preponderance was seen in three families studied by other authors, and in two of these families consanguinity was noted. Recalculating the statistical probability of these findings, Franks and Nance suggested that there exist at least two recessive variants of hereditary unresponsiveness to ACTH: an autosomal form and an X-linked form. Reviewing the presently available literature in the same way as Franks and Nance, we found no evidence for a statistically significant proportion of families with only affected male offspring. Accordingly, genetic heterogeneity has not been demonstrated unequivocally, and autosomal recessive inheritance is the likely pattern of inheritance.

Pathophysiology. Little is known about the pathophysiology of ACTH unresponsiveness. The most striking feature of the disease is the finding of absent or markedly blunted secretion of cortisol coupled with normal production and function of mineralocorticoids in the presence of high levels of ACTH. The other conditions with a similar dissociation between mineralocorticoid and glucocorticoid production are 17α-hydroxylase and 11-hydroxylase deficiencies. Such patients have low cortisol, high ACTH, high levels of mineralocorticoids, hypokalemia, and hypertension from early childhood. None of these latter symptoms was observed in patients with ACTH unresponsiveness.

Plasma ACTH levels have been shown to be greatly elevated both by radioimmunoassay and by bioassay in ACTH unresponsive children. This makes it improbable that a structurally aberrant ACTH molecule is responsible for the disease or that ACTH directed antibodies would interfere with the activity of the hormone. No antibodies to adrenal tissue have been detected in patients.

On pathologic examination, the adrenal glands of most patients studied are atrophic with a dominance of glomerulosa cells and only occasional fasciculata or reticularis cells. In one patient who died at 8 mo, however, the combined weight of the adrenals was 12 g, and marked hyperplasia with lipid congestion was observed, suggesting an enzymatic block. Accordingly, ACTH unresponsiveness may be a heteroge-
neous syndrome. In only one instance has adrenal tissue of such a patient been studied in vitro. The addition of ACTH to slices of this tissue had no effect on cortisol production. Addition of cAMP also produced no change in cortisol production but resulted in a tenfold rise in corticosterone output. These data confirm the glucocorticoid unresponsiveness to ACTH in the adrenal. The increased production of corticosterone in the presence of cAMP may reflect the presence of normal glomerulosa cells. The nature of the defect in ACTH responsiveness is unclear, and it is also unclear whether the anatomical defect in the adrenal is the consequence or the cause of the hormone resistance.

Gonadotropins

The "gonadotropin resistant ovary syndrome" was first delineated as a distinct clinical entity by Jones and De Moraes-Ruehsen in 1969 in a study of three patients with primary amenorrhea. They referred to it as the Savage syndrome after the index case. Since then a number of additional patients with the same or similar disorder have been reported. The main clinical features are amenorrhea and infertility. In half of the reported cases the amenorrhea is primary, and in half it is secondary. Even in the patients with primary amenorrhea, however, secondary sexual characteristics are normally developed. Some patients have slight hirsutism. Gonadotropins are in the menopausal range, whereas estrogens are low or low normal. The histologic pattern in ovarian biopsies differs from that observed in patients with premature menopause in that numerous primordial follicles are present. Few follicles show progression to the antrum stage, and practically none undergo further development. Fibrosis of the superficial stroma has been noted in several cases. All patients have marked hyposensitivity to stimulation with exogenous gonadotropins. Fourteen additional patients with primary amenorrhea, the same histologic picture on ovarian biopsy, and resistance to exogenous gonadotropins have been described by Zourlas. They differ from the other cases described, however, since gonadotropin levels are normal or even low normal.

At present, it is not clear whether this syndrome represents an inherited disease. In most reports, the description of family histories in regard to the presence of consanguinity or of relatives with subfertility, early menopause, or hirsutism is scantly. Recently, it has been reported that a brother of one patient had azoospermia, elevated levels of FSH, normal LH levels, and normal secondary sexual characteristics. In all patients so far investigated, an XX karyotype has been found both in buccal smears and in ovarian tissue. Several patients, however, had developmental defects of the genitourinary tract.

The most striking feature of this syndrome is the developmental arrest of the ovarian follicles at the stage of primordial follicles despite the presence of high endogenous levels of gonadotropins or the administration of large amounts of exogenous gonadotropins. Thus, the disorder is clinically distinct from the form of male pseudohermaphroditism that is associated with an abnormal LH molecule, but it could result either from an abnormal FSH molecule or from some factor that blocks the action of FSH. The fact that some of these patients had apparently normal cycles previously and that the gonadotropin levels were high both by radioimmunoassay and bioassay makes the possibility of an abnormal FSH unlikely. Moreover, no antibodies against FSH have been detected, and no difference has been demonstrated between the molecular weight of the gonadotropins of one of these patients and that of normal menopausal serum. The gonadotropin levels in these patients respond only slightly to clomiphene, but they are enhanced by gonadotropin-releasing factor and suppressed by estrogens, excluding autonomous secretion by a pituitary tumor. No evidence has been obtained for an autoimmune disease.

Accordingly, gonadotropin resistance at the level of the target cells remains the most plausible explanation. There are no data available in regard to the concentration or the characteristics of FSH and LH receptors in these patients. The ability of gonadotropins to stimulate cAMP production in affected ovaries has not been studied. Since the composition and the capacity of the ovary to respond to gonadotropins change in a cyclic way, changes in receptor concentration would not necessarily be due to a congenital defect but could also result from a secondary
disturbance of this cyclic differentiation process. In this context it is of interest that several of the patients received estrogen therapy before the onset of the symptoms. Ovarian refractoriness to gonadotropins is also seen in hyperprolactinemia with or without inappropriate lactation. In at least one patient, prolactin levels were normal. Since estrogens are known to sensitize the ovary to FSH, a disturbance in the production, metabolism, or action of estrogen might form an alternative explanation. Studies performed thus far indicate that these patients metabolize estrogens in a normal way. Recently, however, spontaneous pregnancy during estrogen therapy has been described in two patients with insensitive ovary syndrome. Since the administration of estrogens might have enhanced ovarian responsiveness in those two patients, it remains a possibility that abnormal estrogen metabolism plays a pathogenic role. Unfortunately, the diagnosis of insensitive ovary syndrome was not established by ovarian biopsy in either of these patients prior to treatment.

Insulin

Although there is now abundant evidence that insulin binds to specific high-affinity surface receptors in target tissue cells, the process by which this binding leads to hormone action within the cell is unknown (Fig. 1). Resistance to insulin constitutes the most common clinical disorder of hormone unresponsiveness, and well-documented instances have been described that involve antibodies to insulin, antibodies to the insulin receptor itself, decrease in receptor number, change in receptor affinity for insulin, and abnormalities in the post-receptor apparatus for the hormone. Indeed, resistance to insulin action constitutes a major problem of clinical medicine. In the vast majority of instances this resistance is secondary to the administration of insulin to diabetics or to other pathologic processes as in most forms of obesity, or the resistance plays an uncertain role in the pathogenesis of the disease. These various forms of secondary insulin resistance have been reviewed extensively in the recent past and are beyond the scope of the present paper.

There are, however, several hereditary syndromes in which glucose intolerance is associated with high endogenous levels of insulin and resistance to exogenous insulin, and in which the insulin resistance may be a specific consequence of the mutant genes. These include the Werner syndrome, primary lipodystrophy, familial insulin resistance with somatic abnormalities and pineal hyperplasia, the Alström syndrome, myotonic dystrophy, and leprechaunism.

The nature of the insulin resistance in these syndromes is poorly understood. Insulin binding in lipodystrophy has been reported both as normal and decreased, and insulin binding is normal in circulating monocytes from patients with myotonic dystrophy. Fibroblasts from a patient with leprechaunism contain normal insulin receptor but exhibit a deficiency in the ability to accelerate glucose transport in the presence of insulin, suggesting that the insulin resistance is due to a defect in the coupling mechanism between insulin receptors and the plasma membrane glucose transport system.

From a theoretical standpoint, the most interesting of these diseases is the Alström syndrome, a rare autosomal recessive disease characterized by retinal degeneration that leads to blindness in childhood, nephropathy, acanthosis nigricans, baldness, neural deafness, and mild diabetes associated with insulin resistance and high levels of endogenous insulin. This syndrome may also be accompanied by resistance to vasopressin resulting in a form of nephrogenic diabetes insipidus and resistance to gonadotropins causing hypogonadism. Thus, affected individuals appear to have end-organ unresponsiveness to multiple hormones, suggesting that the pathogenesis may involve either a generalized defect in the plasma membrane or in some component that is common to more than one receptor.

HORMONES WITH INTRACELLULAR RECEPTORS

Steroid and thyroid hormones are poorly soluble in water and are usually transported in plasma bound to carrier proteins. The protein-bound hormones are in dynamic equilibrium with small amounts of free hormones that diffuse by a passive mechanism into cells where they act by fundamentally different mechanisms (Fig. 3) than do the peptide hormones. Inside the
Fig. 3. Mechanism of action of hormones with intracellular receptors. H, hormone; H', activated hormone; R, receptor; R', activated receptor; mRNA, messenger RNA. The numbers in circles refer to possible abnormalities that could give rise to hormone resistance. (1) defect in activation of the hormone, (2) defect in formation of the hormone-receptor complex, (3) defect in activation of the hormone-receptor complex, (4) defective translocation of the activated hormone-receptor complex into the nucleus, (5) defect in binding of the complex to the chromatin, and (6) various post-receptor effector reactions. In the strictest sense, the type-1 abnormality would represent a defect in the capacity to synthesize the active hormone rather than in hormone action.

Androgens

In regard to genetics, pathophysiology, molecular biology, and clinical manifestations, resistance to androgen action is the best understood of all forms of hormone resistance. This in part is due to the fact that mutations that give rise to the disorder are widespread in the animal kingdom so that more than one animal model exists for the study of the disease. In addition, human androgen resistance syndromes are more common than many of the disorders encompassed in this review. The latter feature is the consequence of the fact that most mutations that give rise to the disorders in man (and animals) are X-linked recessive traits and thus inevitably manifest themselves in the hemizygous (XY) state. Further, mutations in androgen action are never lethal in contrast to the effects of severe mutations affecting many other hormones. Although essential for the propagation of the species, normal androgen action presumably is not essential for the life of individuals.

Clinical Features

Male pseudohermaphroditism occurs when genetic males with testes differentiate partially or completely as phenotypic females. Insight into the pathophysiology of the disorder began with the recognition by Morris in 1953 that the most common form of male pseudohermaphroditism, the syndrome of complete testicular feminization (the woman with testes but without body hair),
### Table 4. Known Forms of Androgen Resistance

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Multifetal</th>
<th>Virilization</th>
<th>Urogenital</th>
<th>External</th>
<th>Breast</th>
<th>Testosterone Production</th>
<th>Estrogen Production</th>
<th>LH</th>
<th>5α-Reducase Activity</th>
<th>Dihydrotestosterone Receptor</th>
<th>Findings in Fibroblasts Cultured from Genital Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>5α-reductase deficiency</td>
<td>Autosomal</td>
<td>Absent</td>
<td>Male</td>
<td>Female</td>
<td>Clitoromegaly</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>Normal or increased</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Complete testicular feminization</td>
<td>X-linked</td>
<td>Absent</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Incomplete male pseudohermaphroditism</td>
<td>X-linked</td>
<td>Absent</td>
<td>Variable</td>
<td>Variable</td>
<td>Female</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Post-receptor resistance</td>
<td>Unknown</td>
<td>Absent</td>
<td>Not defined</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

*In one variant enzyme activity is normal under some conditions but inherently unstable.
constitutes a specific inherited disorder. Wilkins subsequently demonstrated that these patients have a profound resistance to the action of both endogenous and exogenous adrogens, a finding that has been confirmed by studies of many parameters of androgen action. Thus, this disorder was the second form of human hormone resistance to be recognized, and an enormous body of information has been accumulated regarding its underlying endocrinology and pathophysiology.

Testicular feminization is the most common form of familial male pseudohermaphroditism, estimates of frequency varying from 1 in 20,000 to 1 in 64,000 male newborns. It is also a common cause of primary amenorrhea, ranking third after gonadal dysgenesis and congenital absence of the vagina. The major clinical features are quite uniform. A phenotypic female is seen by the physician because of inguinal hernia (prepubertal) or primary amenorrhea (postpubertal). The development of the breast at the time of expected puberty, the general habitus, and the distribution of body fat are female in character. Many patients have a truly feminine appearance. Axillary and pubic hair are absent or scanty, but slight vulvar hair is usually present. Scalp hair is that of a normal woman, and facial hair is absent. The external genitalia are unambiguously female, and the clitoris is normal or small. The vagina is short and blind-ending; it may be absent or rudimentary. All internal genitalia are absent except for gonads that have the histologic features characteristic of undescended testes (normal or increased Leydig cell number and seminiferous tubules without spermatogenesis). The testes may be located in the abdomen, along the course of the inguinal canal, or in the labia majora. Occasionally, remnants of mullerian or wolffian duct can be identified in the paratesticular fascia or in fibrous bands extending from the testis.

Plasma testosterone levels and rates of testosterone production by the testes are normal or in some cases higher than in normal men. It is likely that the elevated testosterone production rate is secondary to a high mean plasma LH, which in turn is due to defective feedback regulation because of resistance to testosterone action at the hypothalamic-pituitary level. Elevated LH levels are also probably responsible for the elevated estrogen production by the testes and, thus, for the elevated estradiol concentrations in the spermatic vein blood. In summary, resistance to the feedback regulation of LH production by circulating androgens results in elevated plasma LH levels, and this in turn causes the enhanced secretion by the testes of both testosterone and estradiol. Thus, androgen resistance coupled with enhanced estradiol production results in the development of female secondary sex characteristics at the expected time of puberty as well as the formation of a female phenotype during embryogenesis.

This disorder, which was early recognized as familial, has been shown to be X-linked by Meyer et al. as the result of studies of androgen receptors in fibroblast clones derived from obligate heterozygotes for the disorder. In recent years, several additional single gene mutations that result in androgen resistance and in male pseudohermaphroditism have been described, and it is now clear that partial defects in androgen action can also occur in which the effects on normal male development are minimal. As a result of studies at the clinical, endocrine, and molecular levels, it is now possible to classify these various disorders more precisely than before (Table 4).

The 5α-reductase deficiency (pseudovaginal perineoscrotal hypospadias) was originally described by Nowakowski and Lenz and was subsequently also called familial incomplete male pseudohermaphroditism, type 2. It is a discrete clinical entity in which 46, XY individuals are usually identified as females at the time of birth and have severe perineoscrotal hypospadias with a hooded prepuce, opening of the urethra at the base of the phallus, a blind vaginal pouch of variable size, well-developed and differentiated testes (spermatogenesis may be present), and normal male epididymides, vasa deferentia, and seminal vesicles with termination of the ejaculatory ducts into the blind-ending vagina. The habitus is that of a female without breast development but normal axillary and pubic hair. All female internal genitalia are absent. Most patients are raised as females, but as the result either of the enlarged clitoris at birth or the development of partial virilization at puberty most patients are diagnosed by the time...
of adolescence. As a consequence, castration is usually performed relatively early, with the result that little was known about the natural history of the disorder in the postpubertal period until recently. Consequently, the description by Peterson et al. of 36 affected males from one extended kinship in the Dominican Republic is of unusual interest. At puberty, these individuals undergo virilization with the development of a male muscle pattern, enlargement of the phal- lus and scrotum, and deepening of the voice, but they do not develop gynecomastia. They have erections and are able to ejaculate. Body hair is decreased and the beard growth is scanty. Testicular histology and sperm counts may be normal. The prostate is rudimentary or absent. The disorder is due to the homozygous state of an autosomal recessive gene that causes abnormal sexual development only in 46,XY individu- als. Affected siblings are common, and in several reported families parents were consanguineous. No clear-cut clinical evidence of heterozygous manifestations of the gene has been reported. Gonadotropin levels have been described as being normal or only slightly elevated, and testosterone and estrogen production are those of normal men, providing an explanation for the failure to undergo female breast development at puberty.

Although the expression of the defect in affected individuals with complete testicular feminization and with 5α-reductase deficiency is quite uniform, other families exist in which male pseudohermaphroditism is both incomplete and variable within the same family. The most common presentation is called the Reifenstein syndrome (or familial incomplete male pseudo-hermaphroditism, Type 1). All pedigrees to date are compatible with X-linkage. The usual patient is a male with perineoscrotal hypospa- dias, azoospermia, and gynecomastia that develops at or after puberty. Puberty is characterized by the development of axillary and pubic hair but minimal development of chest and facial hair. Temporal recession of the hairline is usually minimal and the voice is prepubertal in character. More severely affected individuals can have almost complete male pseudohermaphroditism, including incomplete development of the epididymis and vas deferens, formation of a vagina, and incomplete virilization of the uro- genital sinus while less severely affected individu- als may exhibit only a bifid scrotum, sterility, and incomplete virilization at puberty. Indeed, some sterile, but otherwise phenotypic, men have the endocrine and cellular characteristics of partial androgen resistance. The lower ejaculatory duct system has never been charac- terized in the disorder. Cryptorchidism is frequent and the testes are smaller than normal (although usually larger than in the Klinefelter syndrome). The Leydig cells appear normal and the tubules contain both germinal cells and Sertoli cells, but no maturation of the germinal cells beyond the primary spermatocyte is seen. Hyaline degeneration of the tubules is common. Although affected individuals may exhibit ambiguous genitalia at birth, most patients are raised as men. The psychological development in most appears to be unambiguously male and phenotypic men have had successful marriages. Sterility is usual and probably results both from defective spermatogenesis and from the anatomic abnormalities of the ejaculatory system. Urinary gonadotropins are elevated, and plasma LH and plasma testosterone levels are high. Quantitative studies of androgen and estrogen formation and their interconversions have demonstrated findings similar to those described in the complete form of testicular feminization, namely production rates for plasma testosterone and estradiol that are higher than in normal men, and enhanced secretion of estradiol (presumably by the testes) into the circulation. As in complete testicular feminization, it is likely that elevated plasma LH is responsible for the increased secretion of estradiol as well as of testosterone. Although estradiol production is higher on average than in complete testicular feminization, the degree of feminization at puberty is not so pronounced; this is probably because the androgen resistance is incomplete and, as a consequence, the imbalance of the two hormones within the cell is not so severe.

A second clinical form of partial androgen resistance is the syndrome of incomplete testicular feminization. Patients with incomplete testicular feminization resemble patients with testicular feminization except for some degree of ambiguity of the external genitalia and the development of slight virilization as well as
feminization at puberty. The term has been utilized to describe many cases of incomplete testicular feminization, and it is not certain that incomplete testicular feminization is a specific entity. However, some of the patients described under this term constitute a distinct phenotype, and their separation into a distinct androgen resistance syndrome may be justified.\textsuperscript{13}

Affected individuals have the habitus and general appearance of women and, like patients with the complete disorder, most commonly present with primary amenorrhea. The karyotype is 46,XY. Testes are present in the abdomen or in the inguinal canals and on histologic examination are indistinguishable from those in the complete form. The external genitalia are distinctive in that there is partial fusion of the labioscrotal folds and a variable degree of clitoromegaly. The vagina, like that in complete testicular feminization, is short and blind-ending. At laparotomy, all Wolffian duct derivatives are absent, but the presence of Wolffian duct structures is a distinctive feature that (together with the partial virilization of the external genitalia) clearly separates the phenotype from that of complete testicular feminization. Both the upper Wolffian duct structures (epididymides and vas deferens) and the terminal derivatives of the Wolffian ducts—including the ampullae of the vas deferens, the seminal vesicles, and the ejaculatory ducts—are male in character, although underdeveloped in comparison with those of normal men. The ejaculatory ducts terminate in and empty into the vagina.

The frequency of incomplete testicular feminization is uncertain, but in most series it is only about one-tenth as common as the complete form. The family history in most cases is uninformative. Since only a few cases have been diagnosed definitively by excluding deficient androgen synthesis as the cause of the pseudohermaphroditism, it is not certain whether the disorder represents new mutations of a dominant type or whether the case material is too small to demonstrate autosomal recessive or X-linked recessive inheritance. It is of interest that no convincing pedigree has been reported in which complete and incomplete forms of testicular feminization coexist in the same family. The endocrine findings in this syndrome are similar to those in complete testicular feminization.\textsuperscript{213}

Finally, Amrhein and his colleagues have described a form of male pseudohermaphroditism in which the affected individuals resemble patients with testicular feminization but have androgen resistance with normal dihydrotestosterone formation and normal high affinity dihydrotestosterone binding. They are, thus, distinct from the other forms of hereditary male pseudohermaphroditism described in Table 5. Neither the endocrinology nor the genetics of this disorder has been defined.

**Pathophysiology**

In considering the pathophysiology of androgen resistance, it is necessary to review, in brief, normal androgen physiology. The major functions of androgens are the regulation of gonadotropin secretion, the formation of the male phenotype during embryonic development, and the regulation of sexual maturation and function following puberty. The mechanisms by which androgens accomplish these functions are similar to those by which other steroids act (Fig. 3). In brief, testosterone, the principal androgen formed in the testis, circulates in plasma bound to albumin and a specific carrier protein (testosterone-estrogen binding protein). It enters target cells down an activity gradient by what is almost certainly a passive mechanism. Inside the cell, testosterone can be converted to dihydrotestosterone by the 5α-reductase enzyme. Testosterone or dihydrotestosterone is then bound to a specific androgen receptor protein in the cell cytosol, and the hormone-receptor complexes are translo-
cated to the nucleus where they attach to specific sites within the chromatin. As a result, previously dormant genes become available for transcription of RNA, and new messenger RNA and ultimately new protein appear within the cytoplasm of the cell. Current evidence suggests that the testosterone-receptor complex regulates gonadotropin secretion and is responsible for Wolffian stimulation during sexual differentiation and for spermatogenesis. The dihydrotestosterone-receptor complex is thought to be responsible for external virilization during embryogenesis and for the major portion of androgen action during sexual maturation and adult life.2'4

A distinctive feature of androgen physiology is that the hormone acts during embryogenesis to cause development of the male phenotype. In fulfilling this function, androgens actually induce development of those tissues that serve as their major target tissues during postnatal life. As a consequence, resistance to androgen action usually results in major anatomical as well as functional sequelae. Normal sexual development consists of three sequential processes, the establishment of chromosomal (or genetic) sex, the translation of the genetic information into gonadal sex, and finally the development of phenotypic sex.115 In the latter process, indifferent internal and external genitalia are converted to male or female forms, and this process in the male is the direct consequence of hormones secreted by the fetal testis. In the absence of the testes, as in the normal female or in the male embryo castrated prior to the onset of phenotypic sex, differentiation of the wolffian duct proceeds along female lines. Control over the formation of the male phenotype is vested in the action of three hormones. Two of the three (mullerian regression factor and testosterone) are secretory products of the fetal testis. Mullerian regression factor is an incompletely characterized product of the embryonic testis, probably a protein, which acts in the male to suppress the mullerian ducts (the anlage of the uterus and fallopian tubes). Testosterone promotes virilization of the urogenital tract in two ways. It acts directly to stimulate the wolffian ducts to form the epididymis, vas deferens, and seminal vesicle, and it is the precursor for the third fetal hormone, dihydrotestosterone. Dihydrotestosterone, which is formed within the urogenital sinus and lower urogenital tract from circulating testosterone, acts in the urogenital sinus to induce formation of the male urethra and prostate. It also results in the midline fusion, elongation, and enlargement of the genital tubercle, swelling, and folds that eventuate in the development of the male external genitalia. To summarize, in the male embryo, mullerian regression factor prevents development of the uterus and fallopian tubes; testosterone causes formation of the epididymis, vas deferens, and seminal vesicle; and dihydrotestosterone induces development of the prostate, the male urethra, the penis, and the scrotum.

Androgen resistance, by definition, is due to a hereditary defect occurring within the target cell despite normal gonadotropin production and testosterone synthesis. As a result, both the embryonic and postnatal action of androgens are usually deficient. Specific defects have now been identified in the 5α-reductase enzyme, in the androgen receptor, and in the post-receptor effector apparatus of the cell (Table 5).

In patients with 5α-reductase deficiency, the fact that the defective virilization during embryogenesis is limited to the urogenital sinus and the anlage of the external genitalia provided insight into the nature of the fundamental abnormality responsible for the disease. As indicated above, testosterone, the androgen secreted by the fetal testis, appears to be the intracellular mediator for differentiation of the wolffian duct whereas dihydrotestosterone is responsible for virilization of the urogenital sinus and the external genitalia. Consequently, a failure of dihydrotestosterone formation should result in the precise phenotype observed in these patients, namely normal male wolffian duct derivatives but defective masculinization of the structures originating from the urogenital sinus, tubercle, and swelling. In confirmation of this interpretation, dihydrotestosterone formation has been shown to be low in tissue slices of genital skin,206 slices and homogenates of epididymis,206,316 and in monolayers and homogenates of fibroblasts cultured from the foreskin of such patients.217-220 The specific high-affinity binding protein for dihydrotestosterone in the cytosol of foreskin fibroblasts is normal.421 A similar conclusion
regarding the biochemical defect in the disorder was reached by Peterson et al., who showed that the urinary excretion of androsterone (a product of dihydrotestosterone metabolism) was low, as would be predicted if dihydrotestosterone formation were deficient.207

It is of interest that the usual defect in this disorder appears to be an abnormal affinity of the enzyme for testosterone.222 This is of particular interest since, as predicted in Fig. 2, in such a disorder the maximal effect of the hormone might be produced at higher than normal concentrations of the hormone. This may explain why the failure of virilization is incomplete and in particular why virilization at the time of expected puberty (when plasma testosterone reaches the adult level) appears to be more normal than the virilization that takes place during embryogenesis. A second type of the disorder results when the affinity of the enzyme for the cofactor NADPH is abnormal; in this instance the enzyme is synthesized at a normal rate but is inherently unstable.222 As mentioned above, in strict terms 5α-reductase deficiency is not an instance of true hormone resistance, since it is presumed that if dihydrotestosterone were administered at the appropriate time during embryogenesis and at the time of expected puberty, male phenotypic development and function would be normal.

The nature of the androgen resistance in complete testicular feminization has been elucidated only recently. Keenan and coworkers reported that a receptor protein specific for androgen can be demonstrated in fibroblasts cultured from the skin of normal women whereas noncloned fibroblasts from affected individuals showed very low or almost undetectable binding.20,223 a finding that has been confirmed.221,224 The missing receptor is approximately 8–9 S in size.221 Thus, a profound deficiency in the amount of the receptor protein appears to be the common primary defect in the disorder. In contrast, dihydrotestosterone formation in the same cultured fibroblasts is within normal limits.217,218 The profound resistance to both testosterone and dihydrotestosterone can be explained as the result of this single defect. In view of the fact that affected patients do not virilize even slightly when given massive doses of androgen, one would have predicted, according to the formulation of Fig. 2, a defect in the amount of some critical receptor or enzyme, a prediction that is in accord with these findings.

Complete testicular feminization has also been described in the mouse,223 rat,226 cow,227 and dog.228 The disorder in the mouse (Tfm) resembles that of man in that it is X-linked,229 the anatomical defects are almost identical,220 and affected animals are profoundly androgen resistant even during early embryogenesis.229 Studies from several laboratories indicate that the pathogenesis of the androgen resistance in the Tfm mouse is similar to that of the human mutant. Since in the affected animal, as in the human disorder, the androgen-responsive accessory organs of reproduction do not develop, studies in the mouse have focused on two tissues that undergo sexual dimorphism in the postnatal state, namely the kidney and the submaxillary gland. In both tissues of the Tfm mouse there is a deficiency of uptake of radioactive androgen into the nuclear binding sites229,230 and an absence of the high affinity cytosol receptor protein of approximately 8 S size.221,222 Considered together, these studies in affected humans and mice constitute strong evidence that the 8 S dihydrotestosterone-binding protein is in fact the androgen receptor.

Studies designed to examine the molecular basis for the androgen resistance in patients with the Reifenstein syndrome and the syndrome of incomplete testicular feminization have also utilized cultured fibroblasts from genital skin of affected patients. The level of the cytoplasmic androgen receptor protein is low in both disorders, ranging from virtually undetectable in some to levels intermediate between those seen in testicular feminization patients and normal subjects.221,230 In both conditions, dihydrotestosterone formation in the same fibroblasts is normal.217,218 These results suggest that a partial defect in the androgen-receptor protein is the cause of the partial androgen resistance in these incomplete forms of androgen resistance. Since the pathogenesis involves the androgen receptor, the same gene product as in complete testicular feminization and a gene product known to be X-linked, it can be concluded that the inheritance of the Reifenstein syndrome and incom-
plete testicular feminization is also probably X-linked. Recent studies indicate that the partial defect in the androgen receptor in these disorders is in the number rather than the affinity of receptor molecules. Such a finding, in accord with the formulation of Fig. 2 would be expected to result in partial virilization because of a $V_{\text{max}}$ deficit, if the amount of receptor is in fact rate-limiting.

The etiology of the androgen resistance in the post-receptor defect that causes male pseudohermaphroditism is unknown. Since the original description of the disorder by Amrhein and colleagues, two additional patients have been reported. Studies to date indicate that the number and binding affinity of the androgen receptor molecules and the translocation of the hormone-receptor complex into the nucleus are normal. Thus, the defect must lie within the portion of the receptor that is responsible for attachment to chromatin or in one of the subsequent reactions in androgen action (Fig. 3).

**Cortisol**

Complete resistance to the action of cortisol would almost certainly be lethal, but partial resistance has been characterized by Vingerhoeds, Thijssen, and Schwarz in a 55-yr-old man who had markedly elevated levels of plasma cortisol (free and total), elevated 24-hr production rates of cortisol, and elevated plasma ACTH levels. The patient was hypertensive and hypokalemic but had no symptoms or signs of Cushing's syndrome over a 3-yr period of observation. The possibility of the formation of an abnormal steroid was excluded, and it was established that the elevated cortisol secretion was pituitary-dependent and that aldosterone secretion in response to salt loading was appropriate. The authors concluded that the fact that the patient secreted 110–140 mg of cortisol daily for long periods without any evidence of Cushing's disease indicated diminished sensitivity of the peripheral tissues to the glucocorticoid action of the hormone but intact sensitivity to the action of mineralocorticoids. (There is ample evidence that the mechanisms of these two types of effects are different.) Strong support in favor of the thesis was obtained, since treatment of the patient with doses of dexamethasone (which is virtually devoid of mineralocorticoid activity) sufficient to suppress plasma ACTH and diminish cortisol production caused the hypokalemia to disappear. The implication seems clear that the elevated cortisol production in this disorder largely compensates for the partial resistance.

The family of this index patient was also studied; a son, age 20, had hypertension, hypokalemia, and elevated production rates and plasma levels of cortisol. This raises the possibility that the disorder is inherited in an autosomal dominant fashion.

The pathogenesis of the syndrome is unknown. On the basis of careful studies in cultured lymphoma cells there is precedent for several types of resistance to glucocorticoids that could cause such a defect: abnormalities in cytosol receptor protein, abnormalities in the transfer of the cortisol-receptor complex to the nucleus, and abnormalities in the post-receptor effector mechanisms in the cell. Since all human mutations in glucocorticoid action that are compatible with life are likely to be incomplete, assessment of the pathophysiology of the mutation will be difficult.

**Aldosterone**

A special form of congenital renal salt loss associated with insensitivity to mineralocorticoids was described by Cheek and Perry in 1958, and many such patients have been described subsequently. This disorder has come to be known as pseudohypoaldosteronism.

**Clinical Features**

The entire clinical picture was described in the first report; namely an infant who fails to thrive is found to be hyponatremic and hyperkalemic and to lose sodium and chloride in the urine. There is a dramatic clinical response when adequate amounts of saline are administered. Adrenal function and ordinary parameters of renal function are all within normal limits. Renal salt loss usually does not improve following the administration of large amounts of desoxycorticosterone. The authors concluded that the disorder must represent a selective disturbance in the response of the renal tubules to aldosterone under conditions in which the response of the sweat glands may be normal. Variants have been described in which the sweat
and salivary glands and the colon also appear to be involved.\footnote{259}

A special and consistent clinical feature of the disorder is the fact that the salt loss is transitory. Indeed, the initial and subsequent cases were able to thrive without supplemental dietary sodium chloride after the passage of several months, a phenomenon that led some to conclude that the defect could not be in the receptor apparatus for the hormone.\footnote{245} However, Postel-Vinay and colleagues have studied a 9-yr-old patient after the recovery from the salt loss during infancy.\footnote{252} Aldosterone secretion and plasma renin activity were both high and increased further during salt restriction. When spironolactone was administered, urinary and fecal sodium excretion increased. Similar findings have been reported in a long-term follow-up of the original case described by Cheek and Perry.\footnote{260} Thus, the fundamental defect is a hyporesponsiveness to aldosterone that is compensated in part by a massive increase in endogenous production of the hormone.

The initial cases had uninformative family histories and no affected siblings. However, familial occurrence has been recognized more and more frequently in recent reports,\footnote{256} and several families have now been described in which the disorder appears to be inherited in a dominant fashion.\footnote{262} The sporadic cases may be the result of rare, autosomal recessive disorders or new dominant mutations. Indeed, it is not certain whether the disorder represents a single entity in which the clinical variants are the result of variable expressivity or whether there is genetic heterogeneity.

**Pathogenesis**

The pathogenesis is also uncertain. The data are compatible with a partial defect in the aldosterone receptor (either qualitative or quantitative) that can be compensated by increased levels of the hormone. However, in one study, Postel-Vinay et al. were unable to demonstrate an abnormality in nuclear binding of radioactive aldosterone in a colon biopsy from a patient.\footnote{252} The alternative suggestion that the disorder results from a disturbance in sodium reabsorption in the proximal tubule or in the ascending limb of Henle's loop and that the secondary hyperaldosteronism is a compensatory mechanism resulting from volume depletion\footnote{245} is also unlikely since secondary hyperaldosteronism should result in hypocalemia rather than hypercalemia.

The hyperaldosteronism that develops in these patients may compensate in the steady state almost completely for the underlying defect by enhancing distal tubular reabsorption of the salt delivered from the proximal tubule. It is interesting in this regard that Bierich and Schmidt reported a profound defect in Na,K-ATPase in microdissected renal tubules from one patient since this enzyme has been postulated by some to be essential for transcellular movements of sodium and potassium; alternatively, deficient Na,K-ATPase activity may be secondary to defective aldosterone action.\footnote{264}

**Progesterone**

Resistance to the action of progesterone has been described by Keller et al. in a 23-yr-old woman who was evaluated for infertility and whose clinical presentation was similar to that of the inadequate corpus luteum syndrome.\footnote{265} Namely, failure of the endometrial stroma to undergo pseudodecidual reaction was documented in repeated endometrial biopsies during the late luteal phase of the cycle. However, the endometrial biopsy was abnormal during cycles in which the serum patterns of progesterone, estradiol, FSH, and LH were all normal, and exogenous progesterone did not correct the abnormality. In in vitro studies the number of high-affinity progesterone receptors in endometrial cytosol was half that of preparations from normal control subjects. Thus, the incomplete maturation of the endometrial stroma was thought to result from a resistance to progesterone action within the uterus rather than from a deficiency in progesterone formation. Whether this defect was the result of an inherited abnormality is unclear, but it was of interest that there was a family history of female infertility in preceding generations.

**Thyroid Hormones**

Complete resistance to thyroid hormones almost certainly constitutes a lethal mutation. It is not surprising therefore that all forms of thyroid hormone insensitivity characterized to date are incomplete (Table 5).
Clinical Features

The first description of resistance to thyroid hormones was by Refetoff et al.\textsuperscript{266, 267} The index cases were 2 of 6 children of a consanguineous marriage who had congenital sensorineural deaf mutism, nystagmus, delayed bone maturation, stippled epiphyses, goiter, and high circulating \(L\)-thyroxine (\(T_4\)) and \(L\)-triiodothyronine (\(T_3\)) in the presence of a euthyroid clinical state. All standard tests of thyroid function except the basal metabolic rate were those typical for hyperthyroidism. Certain tissues appeared to be resistant to thyroid hormone action: for example, endogenous pituitary thyrotropin secretion was not suppressed completely by the high endogenous levels or by large doses of exogenous \(T_3\) and \(T_4\). Thyroid hormone metabolism was documented to be accelerated, the possibilities of abnormal thyroid hormone synthesis or of abnormal thyroid binding globulin metabolism were excluded, and the formation of triiodothyronine was thought to be normal. The authors concluded that these individuals had an autosomal recessive defect that conveyed a variable degree of resistance to the action of the hormone in different tissues but was partially compensated by excess hormone production. This interpretation is particularly attractive because sensorineural deafness is commonly associated with both acquired and congenital hypothyroidism and with Pendred’s syndrome where goiter and hypothyroidism result from an inborn error in the organification of iodine.\textsuperscript{268} In addition, abnormalities of epiphyseal ossification are known to occur in hypothyroidism.\textsuperscript{266} Thus, it is attractive to assume that all the defects in these siblings were the consequence of incomplete resistance to the action of thyroid hormones. It is of considerable interest that the symptoms in the two original severely affected patients ameliorated with time, indicating that the defect is partially compensated by excess hormone production.\textsuperscript{267}

Subsequently, three unrelated sporadic cases\textsuperscript{269-271} and three additional families with a total of 15 affected individuals have been described.\textsuperscript{272, 275} However, the subsequent cases differ from the original patients in several ways. First, in the latter three families inheritance appears to be either autosomal dominant or codominant rather than by an autosomal recessive mechanism. Second, none of the subsequent patients have had neurosensory deafness or stippled epiphyses, and delayed bone age and goiter are inconstant features. These findings are all consistent with the supposition that these patients have a less severe affliction than do the original patients reported by Refetoff et al.

In addition, three patients have been described with clinical and laboratory features of hyperthyroidism and elevated TSH secretion but no evidence of a TSH-secreting tumor.\textsuperscript{276-278} Administration of thyrotropin-releasing hormone resulted in a marked acceleration of TSH release in each. The administration of triiodothyronine, thyroxine, and dexamethasone lowered serum TSH levels partially. Although it is impossible to exclude the possibility of small pituitary tumors in these patients, the data are compatible with the possibility that the TSH hypersecretion is due to a selective partial resistance of the thyrotrophs of the pituitary to the inhibitory action of thyroid hormones.

Pathophysiology

Considerable information has now been accumulated as to the pathogenesis of hormone resistance in these disorders. In the initial characterizations by Refetoff et al., it was established that the defect cannot lie in the synthesis of an abnormal thyroid hormone, abnormal binding in the plasma, failure of the hormone to penetrate the target cells, failure of conversion of \(T_4\) to \(T_3\), or accelerated hormone degradation.\textsuperscript{266, 267} Furthermore, it was shown, in contrast to some patients with acquired resistance to triiodothyronine,\textsuperscript{14} that no antibodies to triiodothyronine are present. The deduction was then clear that the disorder must lie in the intracellular receptor or effector machinery for the hormone. Subsequent studies by Bernal et al. demonstrated that nuclei of peripheral lymphocytes from the two original subjects bind less than a tenth as much triiodothyronine at high affinity than do nuclei from controls.\textsuperscript{276} Furthermore, the nuclear \(T_3\) binding protein from the patients (but not from controls) did not bind to normal lymphocyte chromatin.\textsuperscript{279}

Subsequent studies of the lymphocytes from less severely affected familial and sporadic cases by Liewendahl et al.\textsuperscript{280, 281} have not succeeded in confirming abnormalities in the nuclear receptor
in these subjects. It is possible that the defect in the nuclear receptor in these mildly affected patients is too subtle to detect by present methods, that the defect lies somewhere in the post-receptor effector mechanisms, or that the disorder is selective and does not involve the peripheral lymphocytes. No studies have been performed to date on the nature of the cellular defect in patients with selective pituitary resistance to thyroid hormones. However, clear-cut evidence for selective resistance to thyroid action in the post-receptor effector mechanisms has been obtained in an experimental animal; York et al. have recently demonstrated that the ob/ob mouse has a selective defect in the ability to increase Na/K ATPase in liver in response to the administration of thyroxine under circumstances in which other parameters of thyroid action are normal.*

Vitamin D

Resistance to Vitamin D has been documented in at least two hereditary forms of rickets. Unfortunately, the terminology that has been applied to these disorders is confusing. What is called vitamin-D resistant rickets is thought to be a disorder in phosphorus metabolism while what is called vitamin-D dependent rickets represents actual resistance to the vitamin. This complicated nosologic issue has recently been reviewed in detail by Rasmussen and Anast.283 For this discussion, we shall focus on the syndromes for which convincing evidence exists that resistance to the action of vitamin D is primary to the pathogenesis of the defect (so called vitamin-D dependent rickets; Table 6).

Clinical Features

Vitamin-D dependent rickets was first segregated from other forms of rickets by Fraser and Salter284 and by Prader et al.285 and many additional patients have been reported subsequently.286-289 The clinical course is similar to that of ordinary rickets due to deficiency of vitamin D except that the history of intake of the vitamin is normal. The onset in infancy is manifested by hypotonia, weakness, growth failure, motor retardation, convulsions, and tetany. Mental retardation may result if patients are not treated early. Pathologic fractures are common. Physical examination reveals the classical findings of rickets including thickening of wrists and ankles, frontal bossing, rachitic rosary, bony deformities, and positive Trousseau and Chvostek signs. X-ray examination reveals the changes of typical rickets, which may be mild to severe. Hypocalcemia, high fecal calcium and impaired calcium absorption are cardinal features. Plasma parathyroid hormone is elevated. Plasma phosphorus may be normal or low, and plasma alkaline phosphatase is elevated, as is urinary cAMP. Plasma 25-hydroxycholecalciferol levels are increased while serum 1,25-dihydroxycholecalciferol is low or undetectable.290-291 This disorder is inherited as an autosomal recessive trait. Parental consanguinity is common. No phenotypic manifestations have been identified in obligate heterozygotes.

It was early recognized that these patients respond to large doses of vitamin D$_2$ or D$_3$ (1.2-2.5 mg/day).284-289 It is now clear that the patients are also resistant to 25-hydroxycholecalciferol but respond to physiologic amounts of 1,25-dihydroxycholecalciferol.292-294

A second form of vitamin D-dependent rickets has been characterized in a 22-yr-old woman with hypocalcemia, secondary hyperparathyroidism, osteomalacia, and osteitis fibrosa cystica who had normal levels of serum 25-hydroxycholecalciferol and fourfold elevated serum 1,25-dihydroxycholecalciferol.295 When this patient was given large amounts of vitamin D, the serum 1,25-dihydroxycholecalciferol increased even further, and the biochemical disorders were corrected.

Pathophysiology

The overall mechanism of action of vitamin D is similar to that of other steroid hormones.283 The basic molecule can either be synthesized in the body (cholecalciferol) or ingested in the form of vitamin D$_3$ (an ergosterol derivative). In either case the vitamin undergoes 25-hydroxylation in the liver to form the 25-hydroxy-derivative and subsequent 1α-hydroxylation in the kidney to form 1,25-dihydroxycholecalciferol, which is currently thought to be the principal active metabolite. This metabolite in turn binds to the cytoplasmic receptor protein, and the steroid-receptor complex is subsequently translocated to the nucleus and bound to the chromatin. As a result, new messenger RNA and proteins
Table 6. Vitamin D-Dependent and Vitamin D-Resistant Rickets

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Response to Vitamin D</th>
<th>Clinical Features</th>
<th>25-hydroxycholecalciferol</th>
<th>Parathyroid hormone</th>
<th>Parathyroid Unifying Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D-dependent rickets type I</td>
<td>Autosomal recessive</td>
<td>YES</td>
<td>YES</td>
<td>+</td>
<td>Increased</td>
<td>LOW</td>
</tr>
<tr>
<td>Vitamin D-dependent rickets type II</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>+</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Vitamin D-resistant rickets</td>
<td>X-linked dominant</td>
<td>No</td>
<td>No</td>
<td>=</td>
<td>Normal</td>
<td>Low</td>
</tr>
</tbody>
</table>
are synthesized, at least some of which appear to be essential for normal calcium transport.

Considerable evidence (albeit indirect) indicates that type-I vitamin-D dependent rickets is the consequence of defective production of 1,25-dihydroxyvitamin D as the result of an inherited defect in the \( \alpha \)-hydroxylase enzyme necessary for its synthesis from 25-hydroxyvitamin D.\(^{290-293}\) The low blood levels of the dihydroxy derivative, normal to high levels of the 25-hydroxy derivative, and the response of patients to replacement doses of 1,25-dihydroxycholecalciferol that appear to be in the physiologic range (around 1\( \mu \)g/day) are in keeping with this interpretation.\(^{290-293}\) Thus, the type-I disorder, like 5\( \alpha \)-reductase deficiency, is not actually due to hormone resistance but rather to incomplete hormone synthesis.

The fact that the patient with the type-II disorder had initially elevated levels of 1,25-dihydroxycholecalciferol but responded when it was raised still further suggests that the defect in this disorder must constitute a partial abnormality somewhere in the receptor-effector machinery.\(^{292}\)

**CONCLUSION**

A common feature of all syndromes of hormone resistance is the presence of a normal or elevated level of the hormone in the circulation. This feature is the inevitable consequence of the fact that every hormone is under some type of regulatory feedback control, and failure of hormone action usually leads to increased hormone production. Since partial defects that can be compensated by increased hormone levels may result in little if any clinical symptoms, hormone resistance should be suspected whenever hormone levels are inappropriately high for the clinical state. It is logical to assume that a large number of defects must go unrecognized because our means of ascertaining such partial defects are still relatively crude. It also follows from this type of reasoning that the partial defects must represent subtle differences in either the number or function of receptor-effector molecules, and consequently the less complete the defect the more difficult it will be to elucidate the molecular pathology.

As summarized in Table 7, genetic heterogeneity of several types is common in these

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Syndrome</th>
<th>Probable Mode of Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiuretic hormone</td>
<td>Nephrogenic diabetes insipidus</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Pseudohypoparathyroidism Type 1 Type II</td>
<td>X-linked or autosomal dominant</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Laron dwarf</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>TSH—unresponsiveness</td>
<td>Autosomal recessive or polygenic?</td>
</tr>
<tr>
<td>Adrenocorticotropin</td>
<td>ACTH—unresponsiveness</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>Gonadotropin—resistant ovary syndrome</td>
<td>?</td>
</tr>
<tr>
<td>Insulin</td>
<td>Werner syndrome</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Androgens</td>
<td>5( \alpha )-reductase deficiency</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Hypercortisolism without Cushing’s disease</td>
<td>Autosomal dominant or polygenic?</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Pseudohypoaldosteronism</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Pseudo-corpus luteum insufficiency</td>
<td>?</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Severe form of thyroid hormone resistance</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Vitamin D-dependent rickets Type 1 Type II</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>
disorders. On the one hand, every known type of human inheritance pattern is represented (autosomal dominant and recessive, X-linked dominant and recessive and polygenic), a relationship that implies that a whole variety of receptor-effector mechanisms have evolved for hormone expression. On the other hand, within each individual syndrome there is also striking heterogeneity (dominant and recessive forms of thyroid hormone resistance). This implies that different steps in hormone action are involved in different forms. At a molecular level the heterogeneity is more striking still when the precise step in hormone action is identified; for example, when examined in sufficient detail every family with male pseudohermaphroditism due to steroid 5α-reductase deficiency has a slightly different mutation. Thus, it may be naive to look for a single defect in a given form of hormone resistance since, like glucose-6-phosphate dehydrogenase deficiency, most mutations may be “private,” differing in each affected family. It follows from this type of analysis that these mutations provide an infinitely large laboratory for studying the various reactions in hormone action. The single gene defects that appear to result in resistance to more than one hormone (pseudohypoparathyroidism, Alström syndrome) may be of particular importance in this regard.

Another type of heterogeneity exists at the level of the target cell. Indeed, it is notable that in individual syndromes and even in individual patients, hormone action may be normal in some target tissues and deficient in others. This relationship implies either that the receptor-effector machinery differs among target tissues, or that it is regulated differently in different target tissues, or that different amounts of the machinery are required for different functions. Elucidation of the mechanism of these various differences should provide insight into exactly how the receptor-effector machinery is regulated at the level of the genes. These differences among target tissues doubtlessly underlie the apparent paradox that in some syndromes, symptoms of hormone resistance can coexist with symptoms of hormone excess (for example the presence of osteitis fibrosa in some patients with pseudohypoparathyroidism).

At the clinical level, the variability in phenotypic expression is more complex than can be explained solely on the basis of the various forms of genetic heterogeneity. (1) It is noteworthy that several of the defects (pseudohypopaldosteronism, resistance to thyroid hormones) appear to ameliorate with age. Since the levels of hormone receptors as well as hormone responsiveness are known to change with age, analysis of the mechanisms of this phenomenon might provide valuable insight into the varying roles of hormones at various stages of development. (2) The capacity of various secondary compensatory responses to overcome or circumvent defects varies markedly among individuals. (3) Environmental factors play a large role in determining the expression of many such defects. For example, varying intake of phosphorus or calcium might influence the clinical expression of pseudohypoparathyroidism.

It is of interest that hereditary resistance syndromes for those hormones that are essential for life (cortisol, ACTH, etc.) are inevitably only partial defects; defects in the action of these hormones that are severe or complete (and thus incompatible with life) are probably eliminated as abortions or stillbirths. Likewise, the more severe the defect (as in the profound hormone resistance of vasopressin-resistant diabetes insipidus and testicular feminization) the less likely the hormone is to be essential for the life of individuals. In this context, the hormones missing from the list of resistance states are noteworthy. For example, resistance to estrogen action has not yet been described. This implies that estrogen action in implantation may be essential for life and that we have not yet recognized partial defects in estrogen action.

Hormone resistance frequently results in anatomical abnormalities (parathyroid hormone, thyroid hormones, growth hormone, insulin, androgens, vitamin D). These anatomical defects would have been anticipated in large part from what is known about deficiency states for the various hormones, but it is noteworthy that partial defects result in less severe anatomical defects. This raises the possibility that many common birth defects (cryptorchidism, hypospadias, skeletal anomalies, deafness) may, in fact, result from subtle defects in hormone action during embryogenesis.

Finally, the information obtained from the
study of patients with hormone resistance has had a spillover effect in basic science, stimulating the development of the concept of hormone receptors. There are other examples (such as the elucidation of the Hardy-Weinberg Law) where basic science has profited from clinical observations. In this instance each patient with hormone resistance provides an opportunity for elucidating the nature of a specific reaction essential for the action of the hormone in question. Indeed, it is conceivable that the analysis of the pathophysiology of the hormone resistance syndromes in man and animals may be as important for understanding eukaryotic control mechanisms as was the analysis of bacterial and viral mutants for the development of biochemistry.

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