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In 1942, Albright and his associates (1) described for the first time a syndrome of true hormone resistance, which they called pseudohypoparathyroidism or Sebright Bantam syndrome.† The classical syndrome of pseudohypoparathyroidism type I encompasses not only clinical hypoparathyroidism with hypocalcemia and hyperphosphatemia, but also certain associated constitutional features, including short stature, round facies, obesity, tendency to mental retardation, shortening of the metacarpal and metatarsal bones, and subcutaneous calcifications. The associated constitutional features have also been designated Albright's hereditary osteodystrophy (AHO). The original authors found that the subjects were resistant to exogenous parathyroid hormone when tested by the phosphaturic response. This test has been replaced by determining the urinary cyclic AMP response to exogenous parathyroid hormone. The latter test more efficiently segregates subjects with classical pseudohypoparathyroidism from normal subjects and from those with other forms of hypoparathyroidism. Albright and his associates, and many others through the years since their original report, proposed a number of hypotheses to explain the biochemical abnormality and mode of inheritance of pseudohypoparathyroidism. Among the hypotheses considered by Albright were end-organ resistance to normally secreted parathyroid hormone, antibodies to parathyroid hormone, and secretion by parathyroid glands of an abnormal peptide capable of blocking the actions of parathyroid hormone (PTH).

The findings of Chase, et al (2) of defective production of cyclic AMP in response to PTH redirected attention to the concept of end-organ resistance and led to the hypothesis that pseudohypoparathyroidism represented a defect in the parathyroid hormone receptor-adenylate cyclase system accounting for end-organ resistance. Subsequent investigations have found that the cell membrane content of the guanyl nucleotide regulatory protein (G-unit that couples receptor activity to adeny-

†Named after the Sebright Bantam cock, which he thought was resistant to androgens. Recently, it has been proved that the female tail-feathering pattern in this variant is not due to resistance to androgens, but rather to an abnormally increased rate of conversion of androgens to estrogens by the skin of these birds (5).

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late cyclase activity) is deficient in most cases of classical pseudohypoparathyroidism with AHO (3,4). Many of the other hypotheses, including antibody to hormone, have been excluded, but recently the concept of an endogenous inhibitor, presumably an abnormal hormone secreted by the parathyroid gland capable of blocking receptors, has once again come under consideration.

Fischer (6) presented data obtained with Chayen to indicate that in the plasma of patients with pseudohypoparathyroidism there is an abnormally high ratio of radioimmunoassayable parathyroid hormone relative to bioassayable parathyroid hormone. Moreover, they have found evidence for inhibitory activity in the plasma of patients with pseudohypoparathyroidism (7). This evidence was determined by adding parathyroid hormone to plasma and carrying out bioassays utilizing the in vitro cytochemical bioassay (CBA) for parathyroid hormone developed by the Chayen group (8). Nevertheless, considerable amounts of bioactive parathyroid hormone have been detected by two groups, Fischer, et al (pp. 459 ff.) and O'Riordan, et al (pp. 469), applying the CBA assay in pseudohypoparathyroidism; and the amounts found overlap the normal and hyperparathyroid ranges.

Another point to consider is that in any condition of excess hormone secretion (primary or secondary hyperparathyroidism) the kidney may develop resistance to the effects of parathyroid hormone. This effect, discussed by O'Riordan, might be attributable to "down regulation" of parathyroid hormone receptors induced by high concentrations of circulating hormone. Part of the hormone resistance in pseudohypoparathyroidism may be due to this down regulation phenomenon. On the other hand, subjects with pseudohypoparathyroidism adequately treated with vitamin D or infused with calcium (to suppress PTH secretion) continue to express the resistance to exogenous parathyroid hormone as determined by urinary cyclin AMP excretion (2). Moreover, one totally parathyroidectomized patient with the disorder persistently displays the urinary cAMP response defect (2). Patients with hormone resistance in vitamin D deficiency show a correction of this defect after treatment (O'Riordan, et al, pp. 469 ff.).

Genetics of pseudohypoparathyroidism

In the past, pseudohypoparathyroidism has been considered a sex-linked disorder. There are few documented cases of male-to-male transmission; the female: male sex ratio in the disorder is approximately 2:1; and pedigrees of families reported appear compatible with the sex-linked transmission mode. On the other hand, a few families do not fit this pattern; some pedigrees seem compatible with autosomal dominant inheritance, others with autosomal recessive transmission (Van Dop and Bourne, pp. 453 ff.).

Part of the confusion concerning heredity stems from the fact that there are too few families with multiple affected members to allow conclusive analysis of inheritance patterns. Also, different investigators use differing parameters to examine patterns of heredity; parameters evaluated include phosphaturia, physiognomy, blood calcium analyses, urinary cyclic AMP responses, and assays for guanylnucleotide (G-unit) regulatory component. Another reason for the confusion is that errors in measured parameters have not uniformly been analyzed statistically. One may arrive at a different conclusion about genetics using the urinary cyclic AMP response on the one hand, or G-unit analyses on the other. Utilizing G-unit analyses, Van Dop and Bourne found evidence that some families with the disorder may represent recessive or dominant autosomal patterns of inheritance. They readily admitted, however, that pedigree analyses reported so far do not rule out X-linked inheritance. Since the G-unit is composed of two subunits, it is possible that the gene controlling one subunit is on the sex chromosome, and the other subunit could be represented on an autosomal chromosome. Such a mechanism might account for apparent diversity in inheritance. Other possible mechanisms are presented below. Another puzzling feature of the inheritance pattern in pseudohypoparathyroidism is that deficiency of the G-unit averages approximately 50% and never approaches, as found in the cyclymphoma cell mutant, total deficiency, which in the human organism might be incompatible with life.

What can one surmise about the biochemical nature of the disorder: deficiency of G-unit or production of abnormal form of hormone? It is difficult to postulate two distinct genetic defects to account for the same abnormality in any given subject. Moreover, production of a defective hormone seems unlikely to account for the generalized defect in hormone responsiveness described by Levine, et al (pp. 464 ff.). Perhaps deficiency of the G-unit, a protein controlling adenylate cyclase in all tissues, can also influence the nature of the product secreted by the parathyroid cell, a process also regulated in part by cyclic AMP. Goltzman (9) has recently described phosphorylated forms of parathyroid hormone. Phospho-proteins are regulated by protein kinases, some of which also are controlled by cyclic AMP. If there was an abnormal distribution of phospho-forms elaborated in pseudohypoparathyroidism due to diminished production of cyclic AMP in the parathyroid cell, one

might be able to explain a link between G-unit deficiency and production of parathyroid hormone forms with varying immuno- to bio-activity. Since cyclic AMP has been implicated in control of chondrocyte function (10), it is also possible that brachydactyly in pseudohypoparathyroidism is another consequence of deficiency of the G-unit in the adenylate cyclase complex.

Classically, autosomal dominant gene defects in heterozygotes produce 50% reductions in enzyme activity, since loss of one of a gene pair yields one half of the normal complement of protein. Fifty percent loss of function in genes carried on the X chromosome might occur in women due to mosaicism, but in affected men the loss of function would be total. This is one of the problems that makes the postulate of sex linkage in pseudohypoparathyroidism difficult; how would one explain thereby male subjects showing 50% of normal complement of the G-unit? Lessons learned in the study of thalassemia may be instructive. In certain forms of beta$^+$ thalassemia (11), the genomic information is normal, but a mutation in an intron causes a splicing defect with consequent abnormal processing of pre-mRNA. The net result is production of significant but reduced amounts of normal beta hemoglobin chains. Such a splicing defect in biosynthesis of G-unit mRNA in pseudohypoparathyroidism, if localized on the X chromosome, could account for 50% or greater reduction in complement of the protein and be compatible with sex-linked inheritance. Studies in thalassemia (11) indicate that similar phenotypic expressions of disease can be caused by many different types of mutations in the genes responsible for hemoglobin synthesis. Like the G-unit, hemoglobin is composed of two different alpha and beta protein subunits. Different genes normally control synthesis of each subunit (still other genes control synthesis of gamma and delta chains, which normally do not operate postnatally). Mutations in either of the genes for alpha or beta chains can cause thalassemia, which may vary in severity from no discernible clinical effect to life-impairing disease. Moreover, compensatory synthesis of fetal hemoglobins, not normally synthesized in the adult, can yield partially effective proteins. Perhaps in pseudohypoparathyroidism will be discovered a similarly remarkable diversity of genetic defects that would account for phenotypic expression of the disorder, which also seems to vary in severity.

Currently, the best single unifying hypothesis to account for the genetic defect of pseudohypoparathyroidism with AHO is a deficiency of production of the G-unit. One must recognize, moreover, that more than one type of inheritance pattern and gene defect may account for the phenotype of this syndrome. Ultimate resolution of these problems depends upon structural determination of the G-unit protein and/or applications of recombinant DNA technology to elucidate the defect at the polynucleotide level.

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