Dwarfism, Hypopituitarism, and Growth Hormone

Small stature or growth retardation is a frequent problem in children, often leading to serious psychological repercussions. In some patients, as for instance in those with achondroplasia, severe hypothyroidism, or classical Turner’s syndrome, the underlying disorder can easily be recognized. More often the growth retarded child presents no other symptoms, and the cause of dwarfism remains obscure in spite of a good history and a careful physical examination. A few years ago, many of these children were treated with anabolic steroids without further investigation. Most of them respond to anabolic steroids with an impressive spurt of growth, but bone maturation is likely to be more accelerated than growth, resulting in a decrease rather than the intended increase in the final height attained. Now hope has turned from the anabolic steroids to growth hormone (GH) which in contrast to anabolic steroids stimulates growth rather than bone maturation.

GH shows a remarkable species specificity in chemical structure and biological activity. In man only human GH (HGH) is effective. The structure of HGH has recently been elucidated (Li, Liu, and Dixon, 1966). It is a polypeptide chain with a molecular weight of 21,500 consisting of 188 amino acids of known sequence. The synthesis of such a large molecule is not yet possible, but it may soon be possible to synthesize a smaller, biologically active part of the original molecule, as has been successfully done with ACTH. At the moment we still depend on HGH extracted from pituitary glands obtained at necropsy. The supply of this material is scarce, and experience with its therapeutic use still limited. So far it seems that dwarfs with supposed deficiency of GH respond with a marked growth acceleration, whereas dwarfs without GH deficiency show only a small or dubious response (Soyka, Ziskind, and Crawford, 1964; Mason and Tanner, 1967). It is, therefore, important to reserve the available HGH for treatment of children with hypopituitarism, and to refuse it to children with dwarfism of other origin.

This raises the question of how to diagnose GH deficiency in children, and this difficult problem is discussed in this issue of the Archives by several authors, Hubble; Stimmmer and Brown; Brown, Stimmller, and Lines; and Clayton, Tanner, Newns, Whitehouse, and Renwick. Most workers in this discipline agree that on clinical grounds alone the diagnosis of GH deficiency can only be suspected, and that the impressive battery of available diagnostic tests solves many but not all diagnostic problems. Some of the tests are, as Hubble points out, time consuming and painful, and need a great deal of cooperation from the patient. Some require a highly specialized laboratory. The results are influenced by the presence or absence of the other anterior pituitary hormones TSH and ACTH. They further depend on the degree of GH deficiency, and on whether the primary disturbance is in the hypothalamus or in the pituitary. These variables explain the discrepancies of results from different centres, and the search for new and better diagnostic tests.

The best simple guide to the diagnosis of GH deficiency is the growth curve, as Hubble, and Clayton and her co-workers have concluded. It begins to flatten at the age of 3 months to 2 years. During the following years it shows an increasing distance from the normal 3rd centile. The bone age is much delayed, but there are no or only questionable clinical symptoms of hypothyroidism. All other clinical findings, such as the mild obesity, the doll-like appearance, the normal body proportions, and sexual infantilism, have little diagnostic value in children. In the absence of neurological and radiological signs of a craniopharyngioma, one has therefore to rely on laboratory tests.

Many but not all patients have a deficiency of TSH and/or ACTH, which is usually only recognized by appropriate functional studies. TSH function is evaluated mainly by PBI and radio-iodine uptake. ACTH deficiency can be recognized with the help of the metyrapone test, the plasma cortisol response to insulin-induced hypoglycaemia, and the water loading test (delay of water excretion, correctable by ACTH). Of these tests the water loading test is the most simple, and the metyrapone test probably the most sensitive. The response of plasma and urine corticoids to a prolonged ACTH test and to vasopressin (vasopressin acting like the corticotrophin releasing factor, CRF) may be normal
in the presence of ACTH deficiency, indicating a
normal pituitary-adrenal axis and pointing to a
hypothalamic origin of the pituitary insufficiency
(Landon, James, and Stoker, 1965; Landon,
Greenwood, Stamp, and Wynn, 1966).

The best way to demonstrate GH deficiency is
probably by the plasma GH response to insulin-
induced hypoglycaemia (Roth, Glick, Yalow, and
Berson, 1963) as discussed in this issue by Hubble
and by Stimmmer and Brown. There are, however,
only a few laboratories which have mastered the
delicate radioimmunological GH assay, and the
results occasionally contradict those from other
tests. Hubble feels that this test does not separate
hypopituitarism from non-hypopituitarism children as
well as the N-retention test. Furthermore, Zimmer-
man, White, Daughaday, and Goetz (1967) have
recently reported two male patients with TSH,
ACTH, and gonadotrophin deficiency, with no
plasma GH response to insulin-induced hypoglyca-
emia, yet with normal stature.

N-retention during a short HGH treatment period
is higher in hypopituitary dwarfs than in control
children (Prader, Illig, Székely, and Wagner, 1964a).
The test is time consuming and tedious but has
diagnostic value (Hubble, 1966, 1967; Brown et al.,
1967). In theory it should tell us whether those
patients with normal stature but without GH
response to hypoglycaemia really lack GH, and
whether the intriguing type of dwarfism with
increased plasma levels of GH (Laron, Pertzelian,
and Mannheimer, 1966) is due to unresponsiveness
to normal HGH, or to the production of an abnormal
and inactive form of HGH. It gives occasionally
misleading values (Prader et al., 1964a; Joss, Rossi,
Zahnd, and Zuppinger, 1966), as do the other tests.
An interesting point is the observation that N-
retention with 10 mg. HGH Raben (Hubble, 1966,
1967; Brown et al., 1967) is the same as with 2 mg.
HGH Raben (Prader et al., 1964a). This confirms
the assumption that the dose response curve is
asymptotic, and that 2 mg. are in or near the
physiological range. In an extension of this short-
term metabolic HGH test, Prader, Zachmann,
Poley, and Illig (1967a) have recently shown that the
serum-a-amino-N increases and the a-amino-N
clearance decreases in hypopituitary dwarfs but not
in control children. These results reflect in part an
increased transport of amino acids through the cell
membranes. Other parameters, like the decrease of
serum urea, the increase of serum phosphorus, and
the increase of urinary calcium, are not significantly
different in the two groups.

The GH response to hypoglycaemia and the N
response to GH are generally regarded as fairly good
tests for distinguishing hypopituitary from non-
hypopituitary dwarfs. This cannot be said for the
insulin tolerance test: in hypopituitarism this test
frequently but not always reveals increased sensitiv-
ity of plasma glucose to insulin, or more strictly, a
decreased responsiveness of plasma glucose to
insulin-induced hypoglycaemia, i.e. a retarded
return of plasma glucose towards fasting values
(Fraser, Albright, and Smith, 1941). Since insulin
should be given intravenously, there is some danger
of severe hypoglycaemia, requiring close observa-
tion of the patient and intravenous glucose if serious
symptoms develop. In the hands of some investiga-
tors this test, or a modification of it, has proved a
useful screening test for recognizing GH deficiency
(Prader et al., 1964a; Trygstad, 1965), while others
find mostly normal results in patients with GH
deficiency (Hubble, 1967; Stimmmer and Brown,
1967; Clayton et al., 1967). It may be that hypo-
glycaemia unresponsiveness is only found when GH
and cortisol are lacking simultaneously. This hypo-
thesis is supported by the normal results obtained on
applying this test to patients with isolated ACTH
deficiency (Odell, 1966), to patients with Addison's
disease that are DOC treated and are well nourished
(Fajans, 1961), and to patients with GH deficiency
but with normal or increased cortisol response to
insulin-induced hypoglycaemia (Stimmmer and
Brown, 1967). In hypopituitary dwarfs, non-
responsiveness to hypoglycaemia can be corrected
by one injection of HGH Raben 2 mg./m.², a
presumably physiological dose (Prader et al., 1967b).

Another diagnostic test proposed is the growth
response to long-term treatment with HGH. In
hypopituitary dwarfs there is a sharp increase in
growth velocity from pretreatment values of 1-4 cm.
per year to values of 5-12 cm. during the first year of
treatment (Raben, 1962, 1965; Soyka et al., 1964;
Prader et al., 1964a; Wright, Brasel, Aceto,
Finkelstein, Kenny, Spauling, and Blizzard, 1965;
Seip and Trygstad, 1966; Prader, Zachmann, Poley,
Illig, and Székely, 1967c; Mason and Tanner, 1967),
whereas no such acceleration has been observed in
non-hypopituitary dwarfs. This test is unfortu-
nately unreliable because of the frequent develop-
ment of HGH antibodies (Trafford, Lillicrap,
and Lessof, 1963; Prader, Wagner, Székely, Illig,
Tomber, and Maingay, 1964b; Parker, Mariz, and Daugh-
aday, 1964). The development of antibodies during
the first months of treatment in sufficient concentra-
tion to block the effect of supposedly physiological
amounts of HGH has been observed in 8 out of 19
patients (Prader et al., 1967c) treated with HGH
Raben, and in at least one patient treated with HGH
Li (Frasier and Smith, 1966). The antibodies have
always appeared during the first 6-9 months of treatment and never later. Since normal HGH should not stimulate the development of antibodies in man, it seems likely that certain extraction and lyophilization procedures alter the HGH molecule, making it antigenic without affecting its biological activity. In this connexion it is interesting to note that growth resistance suggesting GH suppressing antibodies has not been observed in the 12 patients treated with HGH Roos (Seip and Trygstad, 1966).

A. PRADER
Department of Paediatrics
University of Zurich
Zürich, Switzerland

REFERENCES
Fraser, R., Albright, F., and Smith, P. H. (1941). Carbohydrate metabolism. The value of the glucose tolerance test, the insulin tolerance test and the glucose-insulin tolerance test in the diagnosis of endocrinologic disorders of glucose metabolism. J. clin. Endocr., 1, 297.
—— (1967). Diagnosis of hypopituitarism in childhood. ibid., 42, 228.
Landon, J., Greenwood, F. C., Stump, T. C. B., and Wynn, V. (1966). The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin, and the comparison of this procedure with other tests of pituitary and adrenal function. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. J. clin. Invest., 45, 437.
Dwarfism, hypopituitarism, and growth hormone.

A. Prader

Arch Dis Child 1967 42: 225-227
doi: 10.1136/adc.42.223.225