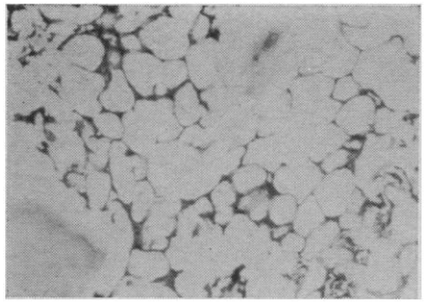

Fig. 2. Pulmonary emphysema in mouse after 317 days of exposure (7 sec/day) to *Alternaria* smoke aerosol. There is distention and attenuation of the alveolar walls (about × 25).

showed emaciation, thickening of the skin about the face, and congestion, edema, and emphysema of the lungs. Histologically, pulmonary emphysema was confirmed (Fig. 2) in the first three mice, two of which also evidenced alveolar cell carcinoma; all four showed secondary or terminal pneumonia, fatty infiltration or vacuolation (or both) and necrosis of the hepatic cells, and hemorrhage, congestion, tubular dilation, and glomerular interstitial nephritis in the kidneys. Four of six mice challenged with *A. niger* smoke developed pulmonary emphysema, among other pathologic changes, by the 8th month. Mice in the corresponding hay-smoke control groups remained normal clinically, and histologic examination of their tissues showed only pulmonary chronic inflammation.

Although *Alternaria* spores and mycelia are present in cigarette, cigar, and pipe tobaccos, there is a much higher percentage of heavy contamination in cigarette tobaccos. It appears significant that pulmonary emphysema was detected grossly in four of four mice exposed repeatedly to *Alternaria* hay-smoke aerosol, and in four of six mice exposed to *A. niger* smoke. Two mice in the *Alternaria* group developed alveolar cell carcinomas, but this incidence may have been fortuitous in that such neoplasms can occur spontaneously.

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Reference

1. *Smoking and Health*, Public Health Service Publ. No. 1103, (U.S. Dept. of Health, Education, and Welfare, 1964).

28 March 1966

Growth-Hormone Deficiency in Man: An Isolated, Recessively Inherited Defect

Abstract. *A deficiency of human growth hormone not associated with other pituitary deficiencies was observed in midgets with sexual ateliosis, a form of dwarfism inherited as an autosomal recessive trait. Body proportions, sexual development, birth weight, and postpartum lactation are normal in this syndrome.*

Gilford (*1*) termed normally proportioned dwarfs, or midgets, ateliotic, and he distinguished sexual and asexual types, depending on the state of sexual development and function. Autosomal recessive inheritance of sexual ateliotic dwarfism was supported by observations of affected sibs, both male and female, with unaffected parents who frequently were related (*2*).

At the same time as Gilford's nosologic contributions, the role of the pituitary in growth became apparent from clinical and experimental observations, and deficient production of a growth-promoting factor by the pituitary was suspected in ateliosis. In the absence of specific methods for assay of growth hormone, as well as the lack of potent, nonantigenic material with which a convincing therapeutic test could be made, pituitary insufficiency could be established only in asexual ateliotics, that is, cases of panhypopituitarism in which the additional deficiency of thyrotropic, adrenocorticotropic, and gonadotropic hormones indicated the pituitary basis of the defect in growth. Probably partly because the cases of panhypopituitarism were almost always nonfamilial (*3*), cases of sexual ateliosis were relegated to an idiopathic group called "primordial dwarfs," the tacit implication being that the defect is not pituitary but is, vaguely conceived, a genetically determined one "at the cellular level."

An isolated growth hormone deficiency has been suspected in some instances (*4*). The experience reported here documents an isolated deficiency of growth hormone in midgets with autosomal recessive sexual ateliosis.

Six sexually mature individuals with proportionate dwarfism were studied. Three (family A) were members of an inbred West Virginia kindred and three (family B) were husband, wife, and daughter (Fig. 1). Their ages ranged from 39 to 77 years, their heights from 123 to 139.5 cm, and their weights from 30.6 to 42 kg. None had a congenital malformation. Bone age was adult in all six. Birth weights, from 2727 to 4545 g, had been normal in all; the midget daughter of two midget parents had a birth weight of 2727 g, cesarean delivery having been performed about 2 weeks before term. Growth retardation was first noted in the first 2 years of life. Five of the six grew gradually, with halt in growth soon after puberty. One of the males had a 20.5-cm growth spurt during puberty, which did not occur until age 25. Secondary sexual characteristics were normal, although puberty was delayed by 2 to 10 years in each. The skin was smooth and wrinkled and appeared abnormally thick. The voices were high-pitched, with a "small" timbre. None had experienced hypoglycemic attacks and all were in general good health.

Extensive clinical, radiologic, and endocrinologic investigations were performed in each. Pituitary trophic hormone production was assessed by the following methods. (i) Thyrotropin (TSH) was assessed by the serum protein bound iodine and I^{131} uptake; (ii) gonadotropin (FSH) by biological activity of urinary extracts with the mouse uterine-weight technique (*5*); (iii) adrenocorticotropin (ACTH) by the presence in the urine of 17-hydroxycorticosteroids and 17-ketosteroids under basal conditions, and on the day of, and the day after the administration of metapirone, 300 mg per 100 pounds of body weight being given every 4 hours for six doses (*5*); (iv) growth hormone (HGH) by a standard human growth hormone immunoassay (*6*) after insulin-induced hypoglycemia and arginine infusions, both potent means of stimulating growth hormone secretion (*6*, *7*). In all six subjects, insulin, given intravenously in a dose of 0.1 unit per kilogram of body weight, produced marked symptoms of hypoglycemia approximately 30 minutes after the insulin administration. Arginine (20 g in 500 ml of water) was infused intravenously over a 30-minute period. The males were given 2.5 mg of stilbestrol twice a day for 2 days prior to the arginine infusion (*7*). Control values for growth hormone were obtained from 15 healthy postpubertal

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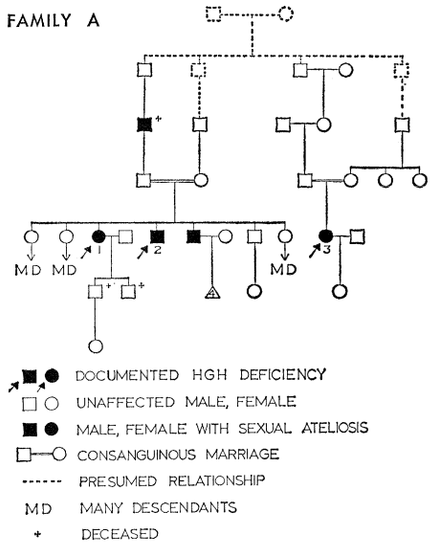
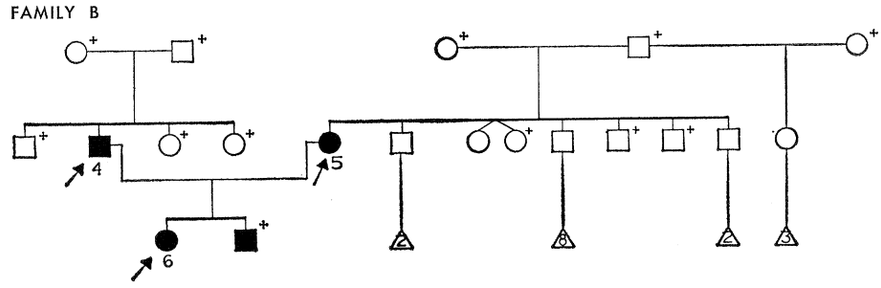


Fig. 1. Pedigrees of families A and B. The evidence for the presumed family lines (----) in family A is excellent, but not yet completely established. One offspring of case 1 died of Hodgkins disease, the other of pneumonia during infancy. Case 6 of family B married a midget and has three children; two are midgets, and one is apparently normal.



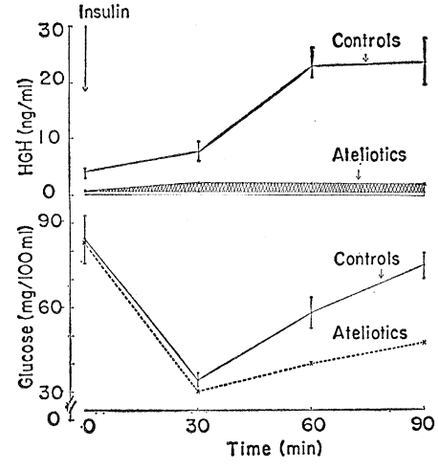
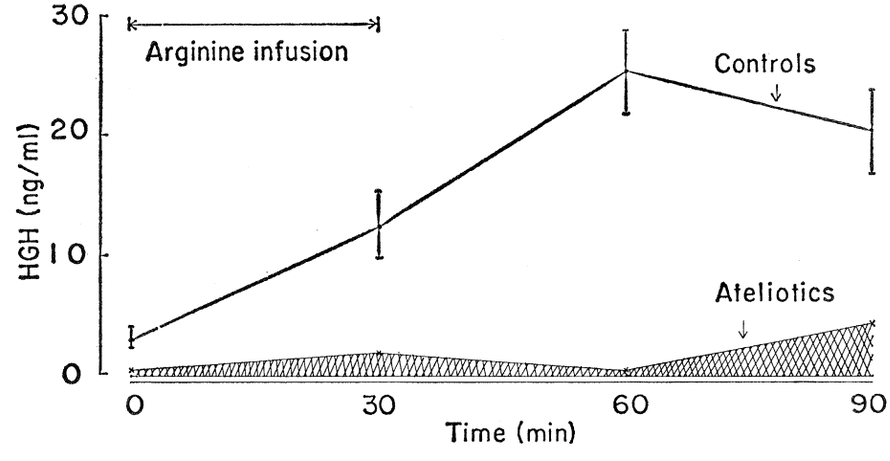


Fig. 2. The crosshatched area represents the total range of response of the six ateliotics. The unbroken line and bars represent the mean (± one standard error of the mean) levels of the controls. (Top) Human growth-hormone and blood-sugar responses after the intravenous administration of insulin (0.1 unit/kg body weight) at zero time. (Bottom) Analysis of human growth hormone after the intravenous infusion of 20 g arginine from time 0 to 30 minutes. The HGH concentration did not rise above 2.5 ng/ml in five of the six ateliotics.



individuals of normal stature, who underwent similar insulin and arginine infusions.

All patients studied had normal secretion of TSH, FSH, and ACTH. All the sexual ateliotics, after fasting, showed a low concentration (1.5 ng/ml or less) of growth hormone in the serum, and the concentration did not rise significantly after insulin-induced hypoglycemia or arginine infusion (Fig. 2). The highest value was 2.0 ng/ml after insulin and 2.5 ng/ml after arginine, except for a single measurement of 5.0 ng/ml in case No. 6, 90 minutes after arginine. In controls there was a mean rise to 23.8 ± 4.0 ng/ml after insulin and to 26.1 ± 3.50 ng/ml after arginine. Glucose changes were comparable in the two groups. These normally proportioned, sexually mature midgets have thus been shown to have an isolated deficiency of human growth hormone, a deficiency which may be homologous to that associated with recessively inherited pituitary dwarfism in mice. Since puberty is often delayed, gonadotropin deficiency cannot be confirmed in a dwarf with growth-hormone deficiency until he is about age 25.

The findings in the two families (Fig. 1) support the view that sexual ateliotic dwarfism is inherited as an autosomal recessive trait. In addition to multiple, affected sibs from consanguineous marriages, the mating of two affected persons resulted in the birth of two similarly affected offspring (Fig. 1, family B). Monotropic growth hormone deficiency was demonstrated in the two parents and one of the offspring; the other affected offspring died accidentally in childhood.

Since all six subjects deficient in growth hormone had normal birth weights, and since all children born to the three females with growth hormone deficiency, including at least one who was herself growth-hormone deficient, weighed over 2700 g at birth, neither maternal nor fetal pituitary growth hormone is probably the major factor responsible for intrauterine growth. Normal intrauterine growth is also a feature of panhypopituitarism (*3*) and of anencephaly, in which the anterior pituitary appears to be at least functionally defective (*8*).

All four growth-hormone–deficient females in this series had normal pregnancies, terminated by cesarean section, and normal lactation. Hence, the human growth-hormone molecule (or at least those parts of it which are immunologically active and are involved

in growth promotion) is not essential to postpartum lactation. Since lactation was also normal in the midget mother of two midget children, it appears that placental lactogen (*9*) is under genetic control separate from pituitary growth hormone or is not necessary for lactation.

Mutations resulting in isolated deficiency of pituitary gonadotropin (*10*), adrenocorticotropin (*11*) or thyrotropin (*12*) probably also occur in man.

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References and Notes

1. H. Gilford, *Med.-Chirurg. Trans.* **85**, 305 (1902).
2. H. Rischbieth and A. Barrington, *Treasury of Human Inheritance*, part VIII, section XV A, 1912.
3. W. H. Daugherty, in *Textbook of Endocrinology*, R. H. Williams, Ed. (Saunders, Philadelphia, 1962), p. 53.
4. J. F. Wilber and W. D. Odell, *Metabolism* **14**, 590 (1965); J. A. Brasel, J. C. Wright, L. Wilkins, R. M. Blizzard, *Amer. J. Med.* **38**, 484 (1965); T. R. Bierich, *Acta Endocrinol. Suppl.* **89**, 27 (1964); H. L. Nadler, L. L. Neumann, H. Gershberg, *J. Pediat.* **63**, 977 (1963); O. Trygstad and M. Seip, *Acta Paediat.* **53**, 527 (1964); T. F. Hewer, *J. Endocrinol.* **3**, 397 (1944); J. M. F. Antonin, *Helv. Paediat. Acta.* **16**, 267 (1961).
5. Dr. Claude J. Migeon, Baltimore, assayed the hormones.
6. J. Roth, S. M. Glick, R. S. Yalow, J. A. Berson, *Science* **140**, 987 (1963).
7. T. J. Merimee, D. A. Lillicrap, D. Rabinowitz, *Lancet* **1965-II**, 668 (1965).
8. D. M. Angevine, *Arch. Pathol.* **26**, 507 (1938); K. Y. Ch'in, *Chinese Med. J. suppl.* **2**, 63 (1938); C. Kind, *Helv. Paediat. Acta* **17**, 244 (1962).
9. S. L. Kaplan and M. M. Grumbach, *J. Clin. Endocrin.* **25**, 1370 (1965).
10. R. L. Biben and G. S. Gordon, *ibid.* **15**, 931 (1955).
11. W. W. Cleveland, O. C. Green, C. J. Migeon, *J. Pediat.* **57**, 376 (1960).
12. A. Querido and J. B. Stanbury, *J. Clin. Endocrinol.* **10**, 1192 (1950).
13. We thank Mrs. B. Smith for technical assistance, Mrs. M. H. Abbott for aid in collecting the genealogies, and Dr. J. O. Humphries for referring case 3. Supported in part by USPHS grant 5-R01-GM 10189. The patients were studied in the Johns Hopkins Clinical Research Center which was supported by USPHS grant 5-M01-FR 35. D.L.R. was supported by a USPHS graduate training grant (5-T1-GM-624) and T.J.M. by a USPHS diabetes training grant (TI-AM-5136).

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Input Resistance, Electrical Excitability, and Size of Ventral Horn Cells in Cat Spinal Cord

Abstract. *Experiments on cat lumbosacral alpha motoneurones showed that, in comparison with cells possessing rapidly conducting axons, the cells with slowly conducting axons have the higher input resistance, that they need weaker stimulating currents to reach the threshold for repetitive firing, and that they need a relatively larger increment in current strength for a given increase in firing rate. Measurements of the number and diameters of dendritic trunks gave larger values for the larger cell bodies. The discussion deals with the interrelation between cell geometry, electrical properties, and the reflex action of alpha motoneurones.*

The alpha motoneurones innervating the hind limb of the cat show, for each motor pool, a continuous variation in the diameter (*1*) and conduction velocity (*2*) of their axons. In previous investigations, the cells with small and slowly conducting axons have often been referred to as "tonic" (or "slow"), and those with large and rapidly conducting axons as "phasic" (or "fast") motoneurones (*2*, *3*). In response to most synaptic inputs, tonic and phasic cells differ markedly with respect to the size of the postsynaptic potentials (inhibitory and excitatory) and to the "reflex threshold" for repetitive firing. In most instances the postsynaptic effects are more pronounced in tonic than in phasic cells (*3–7*), but the reverse situation also occurs (*4*, *8*). With synapses at similar locations, the current generated by a given conductance change (inhibitory or excitatory) would be expected to alter the soma membrane potential more in a cell with a high than in one with a low "input resistance" (*9*), that is, the d-c resistance offered by the cell to the flow of current between an electrode inside the soma and one outside the cell. Thus, less current (for example, a smaller number of active synapses) would presumably be needed for eliciting a repetitive discharge in a cell with a high than with a low input resistance. Therefore, the input resistances of motoneurones with slowly and rapidly conducting axons must be known if the causes for their different reflex behaviors are to be understood (*7*).

The experiments were performed on cats (2.0 to 3.4 kg) anesthetized with pentobarbitone (Nembutal). Single-barreled microelectrodes filled with a solution of 3*M* KCl or 2*M* potassium-citrate were employed for intracellular recording. The dorsal roots caudal to L4 were cut, and various hind-limb nerves were used for antidromic stimulation of the motoneurones. Conduction velocity was calculated from measurements of antidromic latency and conduction distance (*2*). The rectal temperature was generally 37° to 38°C.

For the resistance measurements, rectangular current pulses of variable strength and polarity were injected through the intracellular electrode. Current strength was continuously recorded. A Wheatstone bridge was used to balance out potential changes produced in the microelectrode and the biological structures in series with it (*10, 11*). When the bridge was balanced, the resistance of the microelectrode and the structures in series with it could be read off from the potentiometer of the bridge to within about ± 0.1 Mohm. The input resistance of a motoneurone was determined in one or more of the following ways: (i) by balancing the Wheatstone bridge with the electrode tip inside and just outside the neurone ("direct" method), (ii) by measuring, with the same bridge setting, the potentials produced by currents with the electrode tip inside and just outside the neurone ("direct" method) (*10, 12*), (iii) by measuring the effect of currents on the amplitude of anti- or orthodromic spikes ("spike" method) (*11, 12*), and (iv) by measuring the effect of currents on the spike threshold to an excitatory post-synaptic potential ("threshold" method) (*11, 12*). Methods (ii), (iii), and (iv) have been earlier used and discussed (*10–13*). With many electrodes the "direct" methods could not be used, mainly because the resistance of these electrodes changed on movement through the tissue (*11*). In order to possess a steady state for determining the input resistance (*13*), none of the measurements were performed before at least 0.5 second after the onset of current. Records showing signs of electrode polarization were discarded.

The input resistance was higher in the cells with slowly conducting axons (tonic motoneurones) than in those with rapidly conducting axons (phasic motoneurones). Figure 1 shows the relation between the input resistance of a motoneurone and the reciprocal square of the conduction velocity of its axon. With this latter function of conduction velocity the relation was approximately linear, and the correlation coefficient