

This manuscript is dedicated to Lawson Wilkins, whose intellectual curiosity stimulated so many of his colleagues and students to continue to ask questions and find the answers to the pathophysiology and treatment of congenital adrenal hyperplasia.

REFERENCES

An extended list of references will be supplied upon request. Address to: GGH, Dr. R. Blizzard, 1224 West Main Street, Suite 701, Charlottesville, VA 22901. Telephone: 804-977-8192. Fax: 804-977-9450. E-mail: rblizzard@compuserve.com.

1. Wilkins L, et al. *Bull Johns Hopkins Hosp* 1950;86:249.
2. Barter FC, et al. *J Clin Invest* 1951;30:237.
3. Di-Martino-Nardi J, et al. *Acta Endocrinol (Copenh)* 1986;279(Suppl):305-314.
4. Mulaikal RM, et al. *N Engl J Med* 1987;316(4):178-182.
5. Premawardhana LDKE, et al. *Clin Endocrinol* 1997;46:327-332.
6. Urban MD, et al. *N Engl J Med* 1978;299(25):1392-1396.
7. New MI, et al. *Acta Paediatr Jpn* 1988;30(Suppl):79-88.
8. Clayton GW. *Acta Endocrinol Suppl (Copenh)* 1985;279:295-304.
9. Yu ACM, Grant DB. *Acta Paediatr* 1995;84:899-903.
10. Klingensmith GJ, et al. *J Pediatr* 1977;90:996-1004.
11. Styne DM, et al. In: Lee PA, Plotnick LP, Kowarski AA, Migeon CJ, eds. *Congenital Adrenal Hyperplasia*. Baltimore, Md: University Park Press; 1997:247-259.
12. Thilén A, et al. *Acta Paediatr* 1995;84:894-898.
13. Jääskeläinen J, Voutilainen R. *Pediatr Res* 1997;41(1):30-33.
14. Rasat R. *N Z Med J* 1996;109:311-314.
15. Guo CB, et al. *Clin Endocrinol* 1996;45:535-541.
16. Garner PR. *Semin Perinatol* 1998;22:446-456.
17. Knudsen JL, et al. *Histopathology* 1991;19:468-470.
18. Dittmann RW, et al. *Psychoneuroendocrinology* 1992;17(2/3):153-170.
19. Cameron FJ, et al. *J Clin Endocrinol Metabol* 1995;80:2238-2243.
20. Jääskeläinen J, Voutilainen R. *Clin Endocrinol* 1996;45:707-713.
21. Nass R, Baker S. *J Child Neurol* 1991;6:306-312.
22. Ehrhardt AA, et al. *Johns Hopkins Med J* 1968;123:115-122.
23. Zucker KJ, et al. *Horm Behav* 1996;30:300-318.
24. Money J, et al. *Psychoneuroendocrinology* 1984;9(4):405-414.
25. Ehrhardt AA, Baker SW. In: Friedman RC, Richart RM, Vande Wiele RL, eds. *Sex Differences in Behavior*. New York, NY: Wiley & Sons; 1974:53-76.
26. Ehrhardt AA, Meyer-Bahlburg HFL. *Science* 1981;211:1312-1318.
27. Dittmann RW, et al. *Psychoneuroendocrinology* 1990;15(5&6):401-420.
28. Dittmann RW, et al. *Psychoneuroendocrinology* 1990;15(5&6):421-434.
29. Dittmann RW. *Horm Behav* 1992;26:441-456.
30. Money J, Dalery J. *J Homosexuality* 1976;1:357-371.
31. Meyer-Bahlburg HFL, et al. *Horm Behav* 1996;30:319-332.
32. Sripathi V, et al. *Br J Urol* 1997;79:785-789.
33. Horn P, Hoepffner W. Presented at International Academy of Sex Research, 24th Annual Meeting; June 3-6, 1998; Sirmione, Italy. Abstract.
34. Keely EJ, et al. *Urology* 1993;41(4):346-349.
35. Vanzulli A, et al. *Radiology* 1992;183(2): 425-429.
36. Van Wyk JJ, et al. *J Clin Endocrinol Metab* 1996;81:3180-3190.
37. Laue L, et al. *J Clin Endocrinol Metab* 1996;81:3536-3539.
38. Forest M, et al. *Trends Endocrinol Metabol* 1998;9:284-289.

Abstracts From the Literature

Reconstructing a Human Limb

The vertebrate limb is a very complicated structure whose development is extremely complex. Much has been learned in recent years; however, most articles, even review articles, are not written for clinicians. Bamshad and colleagues at the University of Utah have now assembled a clinician-oriented review that provides many important insights into how human limbs develop and how disturbances that lead to limb defects may arise.

The review covers many areas. It describes how the limb originates in the early embryo and how it grows to its final form. It presents the major actors in the process, many of which have been recently identified because mutations have been detected in patients with limb defects. A few examples include Greig's cephalopolysyndactyly and Pallister-Hall syndromes, which are due to mutations of *GLI3*; ulnar-mammary and Holt-Oram syndromes, which result from *TBX3* and *TBX5* mutations, respectively; Hunter-Thompson and Grebe syndromes, which are caused by *CDMP1* mutations; and Aarskog syndrome due to *FGD1* mutations.

Particular attention is given to 3 groups of genes. *HOX* genes encode transcription factors that contain a 60 amino acid DNA-binding domain called a homeodomain. There are 39 *HOX* genes in humans; these are organized into 4 clusters. *HOX* gene products partly control patterning of many different embryonic structures, including the limbs, where they may subdivide the limb into specific domains and activate downstream genes contingent upon the position of the domain along different axes.

TBX genes also encode transcription factors that share a DNA-binding domain called a T-box. At least 5 *TBX* genes are differentially expressed in the developing limb. In the chick and mouse, *Tbx5* and *Tbx4* are exclusively expressed in the forelimb and hindlimb, respectively, suggesting that they specify or at least influence limb identity. *GLI3* encodes a zinc-finger transcription factor. It seems to have both transcriptional activator and repressor activities. The clinical phenotypes that result from *GLI3* mutations are thought to reflect the combination of these activities that are disturbed. Finally, the authors address the evolutionary aspects of limb development.

Bamshad M, et al. *Pediatr Res* 1999;45:291-299.

Editor's comment: This is a very complete review of the last decade of progress in vertebrate limb development. This review is for the clinician and nonclinician alike and provides considerable insight into the physiology and pathophysiology of limb embryogenesis. The latter is key to understanding physical developmental defects.

One can divide limb development into 2 phases: an early phase during which the essential elements of the limb are formed and a later phase during which the limb grows to reach its final form. This review focuses on the former. Hence, the genes that influence patterning produce the syndromes that reflect defective patterning when mutations occur. In contrast, genes involved in the growth phase are those mutated in osteochondrodysplasias (growth phase defects).

William A. Horton, MD