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RECOGNIZABLE PATTERNS OF HUMAN MALFORMATION

SECOND EDITION

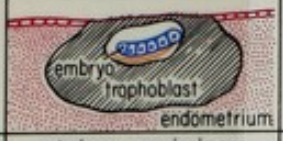
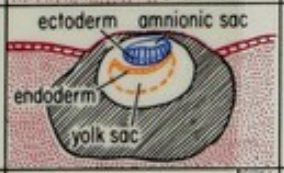
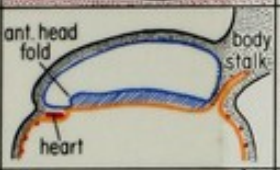
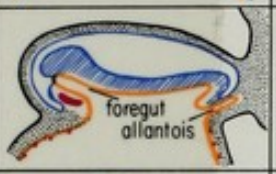
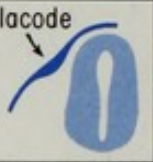
Volume VII in the Series

MAJOR PROBLEMS IN CLINICAL PEDIATRICS

SMITH

0-7216-8376-2

EMBRYONIC DEVELOPMENT

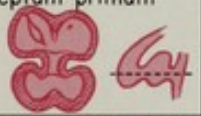
AGE days	LENGTH mm.	STAGE Streeter	GROSS APPEARANCE	C.N.S.	EYE	EAR	FACE
4		III	Blastocyst 				
8	.1	IV					
12	.2	V					
19	1	IX		Enlargement of anterior neural plate			
23	2	X early somites		Partial fusion neural folds 	Optic evagination 	Otic placode 	Mandible Hyoid arches
28	4	XII 21-29 somites		Closure neural tube Rhombencephalon, mesen., prosen. Ganglia V VII VIII X	Optic cup 	Otic invagination 	Fusion, mand. arches 
34	7	XIV		Cerebellar plate Cervical and mesencephalic flexures	Lens invagination 	Otic vesicle 	Olfactory placodes 
38	11	XVI		Dorsal pontine flexure Basal lamina Cerebral evagination Neural hypophysis	Lens detached Pigmented retina 	Endolymphic sac Ext. auditory meatus Tubotympanic recess 	Nasal swellings 
45	17	XVIII		Olfactory evagination Cerebral hemisphere	Lens fibers Migration of retinal cells Hyaloid vessels 		Choana, Prim. palate 
51	22	XX		Optic nerve to brain	Corneal body Mesoderm No lumen in optic stalk		
					Eyelids	Spiral cochlear duct Tragus	

22101907040

QS 615

3676

The embryonic ages for Streeter's stages XII - XXII have been altered in accordance with the human data from Iffy, L. et al: Acta Anat. 66: 178, 1967

EXTREMITIES	HEART	GUT, ABDOMEN	LUNG	UROGENITAL	OTHER
					Early blastocyst with inner cell mass and cavitation (58 cells) lying free within the uterine cavity.
					Implantation Trophoblast invasion Embryonic disc with endoblast and ectoblast
		Yolk sac			Early amnion sac Extraembryonic mesoblast, angioblast Chorionic gonadotropin
	Merging mesoblast anterior to prechordal plate	Stomatodeum Cloaca		Allantois	Primitive streak Hensen's node Notochord Prechordal plate Blood cells in yolk sac
	Single heart tube Propulsion 	Foregut		Mesonephric ridge	Yolk sac larger than amnion sac
Arm bud 	Ventric. outpouching Gelatinous reticulum 	Rupture stomatodeum Evagination of thyroid, liver, and dorsal pancreas.	Lung bud 	Mesonephric duct enters cloaca	Rathke's pouch Migration of myotomes from somites
Leg bud 	Auric. outpouching Septum primum 	Pharyngeal pouches yield parathyroids, lat. thyroid, thymus Stomach broadens	Bronchi 	Ureteral evag. Urorect. sept. Germ cells Gonadal ridge Coelom, Epithelium 	
Hand plate, Mesench. condens. Innervation 	Fusion mid. A-V canal Muscular vent. sept. 	Intestinal loop into yolk stalk Cecum Gallbladder Hepatic ducts Spleen	Main lobes 	Paramesonephric duct Gonad ingrowth of coelomic epith. 	Adrenal cortex (from coelomic epithelium) invaded by sympathetic cells = medulla Jugular lymph sacs
Finger rays, Elbow 	Aorta Pulmonary artery Valves Membrane ventricular septum	Duodenal lumen obliterated Cecum rotates right Appendix	Tracheal cartil. 	Fusion urorect. sept. Open urogen. memb., anus Epith. cords in testicle 	Early muscle
Clearing, central cartil. 	Septum secundum 			S-shaped vesicles in in nephron blastema connect with collecting tubules from calyces	Superficial vascular plexus low on cranium
Shell, Tubular bone 				A few large glomeruli Short secretory tubules Tunica albuginea Testicle, interstitial cells	Superficial vascular plexus at vertex

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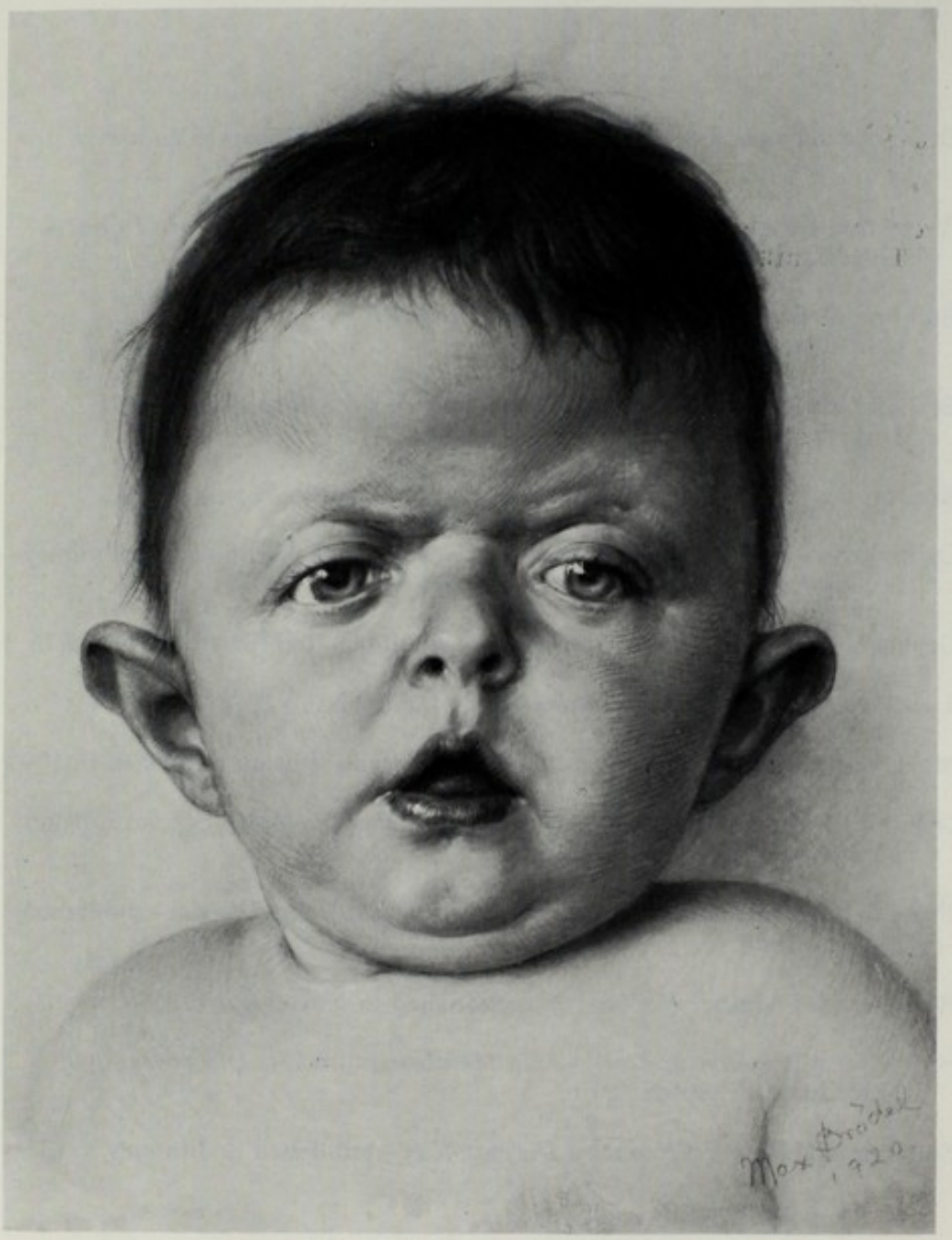
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A Boy with Apert Syndrome

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RECOGNIZABLE PATTERNS OF HUMAN MALFORMATION

Genetic, Embryologic and Clinical Aspects

Second Edition

By

David W. Smith, M.D.

Professor in Pediatrics,
University of Washington School of Medicine,
Seattle, Washington

Volume VII in the Series

MAJOR PROBLEMS IN CLINICAL PEDIATRICS

ALEXANDER J. SCHAFFER
Consulting Editor

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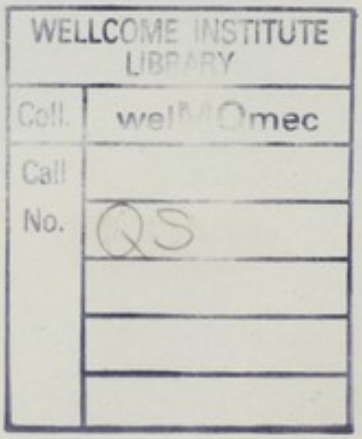
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Dedication

To my wife Ann, beloved inspirational companion.

To my father William H. Smith,
accomplished engineer and would-be physician.

To my teachers Dr. Lawson Wilkins,
molder of clinicians and humanist, and
Professor Dr. Gian Töndury,
complete anatomist, who brings embryology
into living perspective.

Foreword

In his introduction to the first edition of this book, published in 1970, Dr. Smith wrote "It is hoped that the design of this book will lend itself to practical application, as well as providing a basic text for the education of those interested in a better understanding of human morphogenesis." If one may judge from the popularity of that volume and from its constant use by students, residents and practitioners, there can be no question but that it has succeeded in both these aims. But the recognition of more and more constellations of defects, the need to winnow out some which have not proved worthy of special identification and the discovery of the probable causes of a number of others – maternal alcoholism and ingestion of anti-convulsive drugs, for example – have demanded updating at this time. In spite of the winnowing this edition has expanded to include 225 dysmorphic syndromes of multiple primary defects versus 135 in the first edition. There are also new sections on measurement standards, on diagnostic approaches to certain categorical problems, and on psychological aspects of malformation problems. David Smith himself has contributed heavily to this accumulation of knowledge, as all of you who read the pediatric journals surely know. So it is with the utmost pleasure that we present this second edition of Recognizable Patterns of Human Malformation.

ALEXANDER J. SCHAFFER, M.D.

Acknowledgments

The information set forth in this book represents an amalgamation of the knowledge, contributions, and work of many individuals, some of whom are herein recognized.

TEACHERS: Dr. Lawson Wilkins, Johns Hopkins University School of Medicine, whose total clinical approach served as a guide and inspiration toward the development of this book; Dr. Klaus Patau, University of Wisconsin Medical School, from whom the author gained knowledge of cytogenetics and a critical and concise approach toward writing manuscripts; Dr. Gian Töndury, University of Zurich Medical School, from whom the author gained knowledge of embryology and the interpretation of errors in morphogenesis; and Dr. Waldo Nelson, Temple University School of Medicine, whose editorial policy toward clinical relevance and simplicity of semantics has influenced the manner in which this book was developed.

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FELLOWS: Dr. Luc Lemli, Dendermonde, Belgium; Dr. John Opitz, University of Wisconsin Medical School; Dr. Robert Summitt, University of Tennessee Medical School; Dr. Arlan Rosenbloom and Dr. Jaime Frias, University of Florida Medical School; Dr. Jon Aase, Anchorage, Alaska; Dr. Bryan Hall, University of California Medical School (San Francisco); Dr. Kenneth Jones, University of California Medical School (San Diego); and Dr. James Hanson, University of Washington Medical School. Drs. Hall, Jones, and Hanson have been especially helpful in the development of this second edition.

STUDENTS: Dr. Philip Marden, at the University of Wisconsin Medical School; and Dr. John Mulvihill and Dr. Gregory Popich at the University of Washington Medical School.

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text. Her dedication and capacity for obtaining even the most obscure references are greatly appreciated. Gerald J. Oppenheimer, Head Librarian at the University of Washington Medical School Library, has been most helpful, allowing a special room for this project.

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MEMORIAL: The Robert Gordon Schneller Memorial Fund provided funds for medical illustration and photography for the first edition of this text, which greatly enhanced the educational value of this book. Mr. and Mrs. M. R. Schneller had two sons. Robert Gordon, a student at the University of Washington, was interested in problems of malformation, at least partially because his younger brother has Down's syndrome. Robert's life and his interest were cut short by a mountaineering accident at the age of 20 years. Mr. and Mrs. Schneller hope, as do I, that the contribution of his friends and relatives may assist in stimulating others to pursue the interest which Robert had in extending our knowledge about malformation problems.

DAVID W. SMITH, M.D.

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INTRODUCTION

including dysmorphology approach and classification

We ought not to set them aside with idle thoughts or idle words about "curiosities" or "chances." Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question – why is it rare? or being rare, why did it in this instance happen? – JAMES PAGET, Lancet, 2:1017, 1882.

The questions set forth by Paget are still applicable today. Every malformation represents an inborn error in morphogenesis. Just as the study of inborn metabolic errors has extended our understanding of normal biochemistry, so the accumulation of knowledge concerning defects in morphogenesis may assist us in further unraveling the story of structural development.

The major portion of this text is devoted to patterns of malformation. You will also find relevant chapters on normal and abnormal morphogenesis, genetics and genetic counsel, minor anomalies and their relevance, a clinical approach toward a specific diagnosis for certain categorical problems, and normal standards of measurement for a variety of features. It is hoped that the design of the book will lend itself to practical clinical application, as well as provide a basic text for the education of those interested in a better understanding of alterations in morphogenesis. Furthermore, many of the charts have been developed for direct use in the counseling of patients and parents.

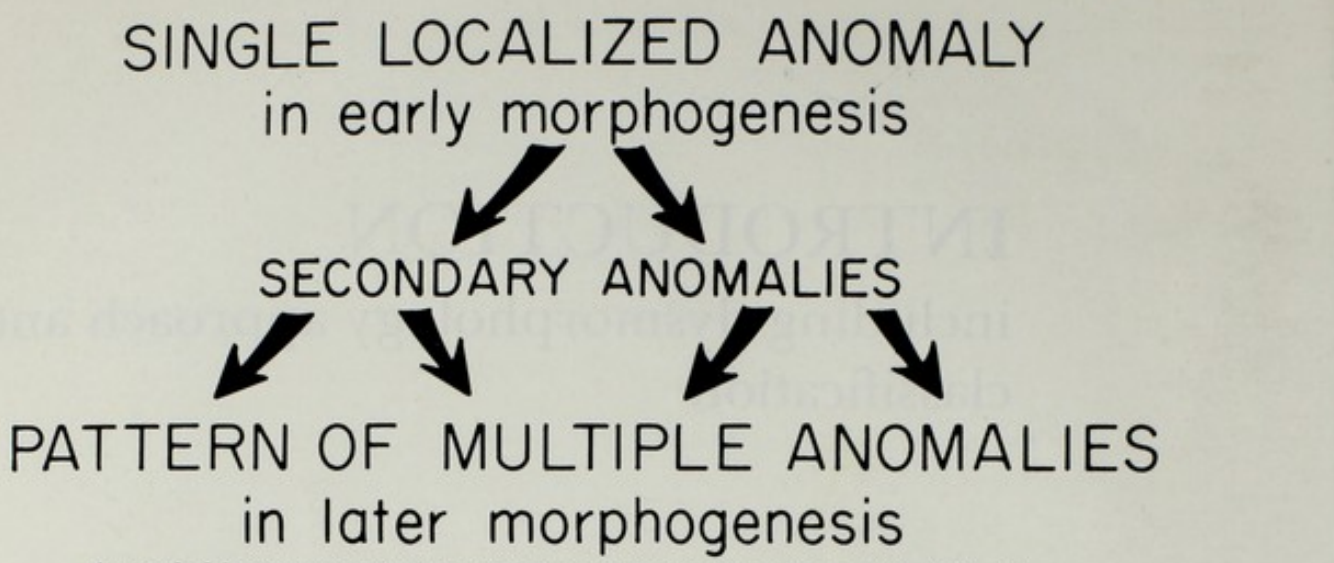
Accurate diagnosis of a specific syndrome among the 0.7 per cent of babies born with multiple malformations is a necessary prerequisite to providing a prognosis and plan of management for the affected infant, as well as genetic counseling for the parents.

The following is the author's approach toward the evaluation of an individual with multiple defects:

DYSMORPHOLOGY APPROACH

I. Gather information. The family history is an essential aspect of such an evaluation. Such a question as "Are there any individuals in the family with a similar type of problem?" may be helpful. The early history should usually include information about the onset and vigor of fetal activity, gestational timing, mode of delivery, size at birth, neonatal adaptation and postnatal development, growth, and problems. The physical examination should be complete, searching for minor as well as major anomalies. When possible, measurements should be taken to determine whether a given feature such as apparent ocular hypertelorism, small appearing ear, etc., is truly abnormal. The charts of normal measurements in Chapter 7 are for this purpose. An unusual feature should ideally be interpreted in relation to the findings in other family members before determining its relevance.

II. Interpret the patient's anomalies from the viewpoint of developmental anatomy and strive to answer the following questions:
   A. Which anomaly in the individual represents the earliest defect in morphogenesis? A table for this purpose is found in Chapter 4. From such information one can determine that the problem in development must have existed *prior* to a particular prenatal age and any factor *after* that time could not be the cause of that malformation.
   B. Is a given defect primary or secondary? Morphogenesis is a timely and sequential process in which a defect of one structure may compromise the formation



Anomalad designates a single localized anomaly plus its subsequently derived structural consequences, as depicted above.

of subsequent structures and result in a cascade of secondary anomalies, referred to as an anomalad. An attempt should be made to determine the primary anomalies. This approach will tend to subdivide the multiple defect patients into two general categories:

1. Those having a *single anomalad* in which the pattern of defects is the consequence of a single localized malformation which anteceded and was the cause for the secondary defects. This concept is set forth in Figure 1.
2. Those having *multiple primary anomalies,* either within many areas of one system or involving multiple systems.

III. Attempt to arrive at a specific overall diagnosis, confirm when possible, and counsel accordingly. When possible, counsel should include the following: an understanding of how the altered structures came to be as they are; the natural history of the condition and what measures can be utilized to assist the child; and the mode of etiology and the genetic counsel (recurrence risks).

IMPORTANT GENERAL PRINCIPLES

The following are some of the important principles and information which should be appreciated in the evaluation of a patient with multiple defects.

1. Nonspecificity of Individual Defects

With rare exceptions a clinical diagnosis of one of these patterns of malformation cannot be made on the basis of a single defect, as is evident in the tables in Chapter 2. Even a rare defect may be a feature in several syndromes of variant etiology. A specific diagnosis is usually dependent on recognition of the overall *pattern of anomalies,* and the detection of minor defects may be as helpful as major anomalies in this regard.

2. Variance in Expression

Variance in extent of abnormality (expression) among individuals with the same etiological syndrome is a usual phenomenon. Except for such nonspecific general features as mental deficiency and small stature, it is unusual to find a given anomaly in 100 per cent of patients with the same etiological syndrome. For example, in full 21 trisomy Down syndrome only mental deficiency is ubiquitous; hypotonia is a frequent feature, but most of the other individual clinical features are found in less than 80 per cent of such patients. However, a specific diagnosis of Down syndrome can generally be rendered, based on the *total pattern of anomalies.*

Intraindividual variability in expression is also frequent, with variance in the degree of abnormality on the left versus the right side of the individual.

3. Heterogeneity

Similar phenotypes (overall physical similarity) may result from *different* etiologies. Only by finer discrimination of the phenotype or mode of etiology can such similar entities be distinguished. For example, the Marfan syndrome and homocystinuria were initially discriminated on the basis of homocystinuria, next by a difference in mode of etiology (autosomal dominant for the Marfan syndrome and autosomal recessive in homocystinuria), and finally by closer scrutiny of the phenotype. As another example, achondroplasia is frequently misdiagnosed among individuals who have chondrodystrophies which only superficially resemble true achondroplasia. A diagnosis should be rendered only when there is close resemblance in the overall pattern of malformation between the patient and the disorder under consideration.

4. Etiology

Most of the disorders herein set forth have a genetic basis. Chapter 5 provides the back-

ground information relative to genetic counseling for these conditions.

Besides the following established disorders, roughly half the individuals with multiple defects have conditions which have not yet been recognized as a specific syndrome. A small percentage of such patients (8 per cent in Summitt's study)* have a structural chromosomal abnormality. In such cases genetic counsel should be withheld until it has been determined whether either parent is a balanced translocation carrier of the chromosomal abnormality. In the absence of an evident chromosomal abnormality or familial data suggesting a particular mode of etiology, it is generally impossible to state any accurate risk of recurrence for unknown patterns of multiple malformation. It is presumptuous to inform the parents that "this is a rare condition and therefore unlikely to recur in your future children." Under these circumstances the author's present approach is to inform the parents that the lowest recurrence risk is zero and the highest risk with each pregnancy would be 25 per cent. The latter figure is predicated on the possibility of recessive inheritance or a nondetectable chromosomal abnormality from a balanced translocation carrier parent.

The recommendations of an international committee on "Classification and Nomenclature of Morphologic Defects," published in *Lancet, 1*:513, 1975, were predominantly utilized in this text. The manuscript had already been sent to the publisher and therefore it was difficult to make all of the changes which had been recommended.

These recommendations were set forth at a meeting held on February 10th and 11th, 1975, at the National Institutes of Health in Bethesda, Maryland, to discuss further the tentative suggestions for classification, nomenclature, and naming of malformations published in *Lancet*, April 27, 1974. The meeting was initiated by Dr. Richard L. Christiansen and attended by the planning consultants: Dr. David Smith (Seattle, Washington), chairman; Dr. Murray Feingold (Boston, Massachusetts); Dr. Robert G. Gorlin (Minneapolis, Minnesota); and Dr. David E. Poswillo (London, England); and the following participants: Dr. Dagfinn Aarskog (Bergen, Norway); Dr. Daniel Bergsma (White Plains, New York, U.S.A.); Dr. M. Michael Cohen, Jr. (Seattle, Washington, U.S.A.); Dr. Peter Dunn (Bristol, England); Dr. David Erickson (Atlanta, Georgia, U.S.A.); Dr. Pierre E. Ferrier (Geneva, Switzerland); Dr. F. Clarke Fraser (Montreal, Canada); Dr. Richard Goodman (Tel-Hashomer, Israel); Dr. R. B. Lowry (Vancouver, Canada); Dr. Victor A. McKusick (Baltimore, Maryland, U.S.A.); Dr. Carol Newton (Los Angeles, California, U.S.A.); Dr. John M. Opitz (Madison, Wisconsin, U.S.A.); Dr. Eberhard Passarge (Hamburg, Germany); Dr. Robert R. Sokal (Stony Brook, New York, U.S.A.); Dr. Ray E. Stewart (Los Angeles, California, U.S.A.).

The objectives were to suggest a flexible, practical, yet scientific nomenclature which could be used by clinicians as the basis of a universal classification – a classification which may be incorporated with the International Classification of Disease of the WHO skeleton classification, and also be capable of expansion to meet the needs of the scientist working in the field of birth defects. By agreeing on a specific nomenclature and by establishing the basis for a classification, it was hoped to improve identification of malformation, data storage, and retrieval of information.

GENERAL NAMES

1. ***Malformation*** – a primary structural defect that results from a localized error of morphogenesis, e.g., cleft lip.
2. ***Deformation*** – an alteration in shape and/or structure of a previously normally formed part, e.g., torticollis.
3. ***Anomalad*** – a malformation together with its subsequently derived structural changes, e.g., Robin anomalad.
4. ***Malformation Syndromes*** – recognized patterns of malformation presumably having the same etiology and currently not interpreted as the consequence of a single localized error in morphogenesis, e.g., Down syndrome.
5. ***An Association*** – a recognized pattern of malformations which currently is not considered to constitute a syndrome or an anomalad. As knowledge advances, an association may be reclassified as a syndrome or as an anomalad, e.g., hemihypertrophy with Wilms tumor.

Classification of Multiple Malformations

I. Syndromes
  A. Known etiology
    1. Chromosome abnormality
    2. Gene abnormality
      a. Known biochemical defect
      b. No known biochemical defect
    3. Environmental factor
  B. Etiology not established
II. Anomalads
III. Associations
IV. Combination of malformations not assigned to any of the above categories

Naming of Single Malformations

Utilize adjective or descriptive term and the name of the structure or the classical equivalent in common use: e.g., small mandible or micrognathia.

*R. L. Summitt, Cytogenetics in mentally defective children with anomalies: a controlled study. J. Pediatr., *74*:58, 1969.

NAMING OF PATTERNS OF MALFORMATIONS

1. When the etiology is known and easily remembered, utilize the appropriate term to designate the disorder.
2. Continue time-honored designations unless there is good reason for change.
3. In the absence of a reasonably descriptive designation, eponyms, some of them multiple, may be used until the basic defect for the disorder is recognized. However, usage of an eponym should, in the future, be limited to one proper name.
4. The possessive use of an eponym should be discontinued since the author neither had nor owned the disorder.
5. Designation of a disorder by one or more of its manifestations does not necessarily imply that they are either specific or consistent components of that disorder.
6. Avoid names which may have an unpleasant connotation for the family and/or affected individual.
7. The syndrome should not be designated by the initials of the originally described patients.
8. Names which are too general for a specific syndrome should be avoided.
9. Avoid acronyms unless extremely pertinent or appropriate.

Considerable discussion centered at this meeting on names for many of the more common patterns of malformations. While there was often unanimity in the choice of a name it was not always possible to obtain agreement by strict observance of the above guidelines because of preference for time-honored designations. The group generally expressed the hope that the guidelines would be observed in future naming of patterns of malformation, and that consideration be given to the incorporation of these proposals in the next revision of the International Classification of Disease.

Examples of recommended names:

Syndromes:
- Chromosome abnormality (subclassified by karyotype):
  - Trisomy 21, or Down syndrome
  - Trisomy 18 syndrome
  - Trisomy 13 syndrome
  - Turner syndrome
  - Klinefelter syndrome
- Gene abnormality:
  - Neurofibromatosis
  - Tuberous sclerosis
- Environmental:
  - Congenital rubella syndrome
  - Congenital alcohol syndrome
- Etiology not established:
  - de Lange or Cornelia de Lange syndrome
  - Russell-Silver syndrome
  - Noonan syndrome
  - Beckwith-Wiedemann syndrome
  - Williams syndrome
  - Prader-Willi syndrome

Anomalads:
- Abdominal muscle deficiency anomalad
- Holoprosencephaly anomalad
- Robin anomalad

It was hoped that in the future attention will be given to nomenclature for less common patterns of malformation, and for single anomalies. Interest was shown in the possibilities of the application of new methods in taxonomy for the analysis of birth defects. Comments concerning these guidelines should be directed to Dr. Richard L. Christiansen, Chief, Craniofacial Anomalies Program, National Institute of Dental Research, Westwood Building, Room 520, Bethesda, Maryland 20014, U.S.A.

METHOD AND UTILITY OF PRESENTATION OF PATTERNS OF MALFORMATION

The arrangement of the disorders in this book is predominantly based on the similarity in overall features or in one major feature among the patterns of malformation, as set forth in the table of contents. Thus, the order of presentation is designed to be of assistance in the diagnosis of the patient for whom a firm diagnosis has not been established. With the exception of the chromosomal abnormality syndromes which share many features, and the disorders determined by an environmental agent, the conditions are not arranged in accordance with the mode of etiology. An initial alphabetical listing of the more commonly used designations for these patterns of malformation is presented to aid the reader.

Each syndrome or anomalad has a listing of anomalies. The three features which together tend to distinguish the syndrome from other known disorders are set forth in bold print. The main list consists of defects which occur in at least 25 per cent and usually more than 50 per cent of patients. Sometimes the actual percentage or number is stated for each anomaly. Below these are listed the occasional defects that occur with a frequency of from 1 to 25 per cent, most commonly 5 to 10 per cent. The occurrence of these "occasional abnormalities" is of interest and has been loosely ascribed to "developmental noise." In other words, an adverse influence that usually causes a particular pattern of malformation may occasionally cause other anomalies as well. Possibly it is differences of genetic background, environment, or both that allow some individuals to express these "occasional" anomalies. The important feature is that they are not random for a particular syndrome. For example, clinicians who have seen a large number of

children with the Down syndrome are not surprised to see "another" Down syndrome baby with duodenal atresia, web neck, or tetralogy of Fallot.

The references listed for each syndrome or anomalad have been selected as those that give the best account of that disorder, provide recent additional knowledge, or represent the initial description.

A word of caution is indicated. This book does not contain a number of syndromes, especially those reported after April, 1974.

OTHER SOURCES OF INFORMATION

In addition to this text, there are many others which may be of value in the recognition, management, and counsel of particular problems and patterns of malformation.

General

Bergsma, D. B.: Birth Defects Atlas and Compendium. Baltimore, Williams and Wilkins Co., 1973.

Gorlin, R. J., Cohen, M. M., Jr., and Pindborg, J. J.: Syndromes of the Head and Neck, 2nd ed. New York, McGraw Hill Co., 1975.

McKusick, V. A.: Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes. Baltimore, The Johns Hopkins Press, 1974.

Warkany, J.: Congenital Malformations. Chicago, Year Book Medical Publishers, 1971.

Connective Tissue, Skeletal Dysplasias, Orthopedic

Bailey, J. A.: Disproportionate Short Stature. Philadelphia, W. B. Saunders Co., 1973.

McKusick, V. A.: Heritable Disorders of Connective Tissue, 4th ed. St. Louis, C. V. Mosby Co., 1972.

Spranger, J. W., Langer, L. O., and Wiedemann, H.-R.: Bone Dysplasias, an Atlas of Constitutional Disorders of Skeletal Development. Philadelphia, W. B. Saunders Co., 1974.

Temtamy, S., and McKusick, V. A.: Synopsis of hand malformations with particular emphasis on genetic factors. *In* Clinical Delineation of Birth Defects, Vol. IV, edited by D. S. Bergsma and V. A. McKusick. Baltimore, Williams & Wilkins, 1969, pp. 125–184.

Wynne-Davies, R.: Heritable Disorders in Orthopedic Practice. Oxford, Blackwell Scientific Publications, 1973.

Mental Deficiency with Associated Anomalies

Gellis, S. S., and Feingold, M.: Atlas of Mental Retardation Syndromes. Washington, D.C., U.S. Government Printing Office, 1968.

Holmes, L. B., et al.: Mental Retardation: An Atlas of Diseases with Associated Physical Abnormalities. New York, The Macmillan Co., 1972.

Hereditary Deafness with Associated Anomalies

Konigsmark, B. W.: Syndromal approaches to the nosology of hereditary deafness. *In* Clinical Delineation of Birth Defects, Vol. VII, edited by D. S. Bergsma and V. A. McKusick. Baltimore, Williams & Wilkins, 1971, pp. 2–17.

Ocular Abnormalities

Waardenburg, P. J.: Genetics and Ophthalmology, Vols. I and II. Oxford, Blackwell Scientific Publications Ltd., 1963.

Facial Clefting

Gorlin, R. J., Cervenka, J., and Pruzansky, S.: Facial clefting and its syndromes. *In* Clinical Delineation of Birth Defects, Vol. VII, edited by D. S. Bergsma and V. A. MsKusick. Baltimore, Williams & Wilkins, 1971, pp. 3–49.

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Chapter One

RECOGNIZABLE PATTERNS OF MALFORMATION

A. Chromosomal Abnormality Syndromes

DOWN SYNDROME

(Trisomy 21 Syndrome)

Hypotonia, Flat Facies, Slanted Palpebral Fissures, Small Ears

Down's[1] report of 1866 on the ethnic classification of idiots stated that a "large number of congenital idiots are typical Mongols," and he set forth the clinical description of the Down syndrome. The textbook by Penrose and Smith[2] provides an overall appraisal of this disease which has an incidence of 1 : 660 newborns, making it the most common pattern of malformation in man. A book has recently been written for parents of Down syndrome children,[3] providing them with a background as to the cause, the nature and natural history, and the adaptation of the child with Down syndrome.

ABNORMALITIES

General. Hypotonia with tendency to keep mouth open and protrude the tongue; diastasis recti.
Hyperflexibility of joints.
Relatively small stature with awkward gait.

Central Nervous System. Mental deficiency.

Craniofacial. Brachycephaly with relatively flat occiput, and tendency toward midline parietal hair whorl. Mild microcephaly with upslanting palpebral fissures.
Thin cranium with late closure of fontanels.
Hypoplasia to aplasia of frontal sinuses, short hard palate.
Small nose with low nasal bridge, and tendency toward inner epicanthal folds.

Eyes. Speckling of iris (Brushfield's spots) with peripheral hypoplasia of iris.
Fine lens opacities by slit lamp examination (59 per cent).
Refractive error.

Ears. Small, overfolding of angulated upper helix; sometimes prominent; small or absent earlobes.

Dentition. Hypoplasia, irregular placement, *less* caries than usual.

Neck. Appears short.

Hands. Relatively short metacarpals and phalanges.

Fifth finger: hypoplasia of midphalanx of fifth finger (60 per cent) with clinodactyly (50 per cent), a single crease (40 per cent), or both.
Simian crease (45 per cent).
Distal position of palmar axial triradius (84 per cent).
Ulnar loop dermal ridge pattern on all digits (35 per cent).

Feet. Wide gap between first and second toes.
Plantar crease between first and second toes.
Open field dermal ridge patterning in hallucal area of sole (50 per cent).

Pelvis. Hypoplasia with outward lateral flare of iliac wings and shallow acetabular angle.

Heart. Anomaly in about 40 per cent; atrioventricular communis, ventricular septal defect, patent ductus arteriosus, auricular septal defect, and aberrant subclavian artery, in decreasing order of frequency.

Skin. Loose folds in posterior neck (infancy).
Cutis marmorata, especially in extremities (43 per cent).
Dry hyperkeratotic skin (with time) in 75 per cent.

Hair. Fine, soft, and often sparse; straight pubic hair at adolescence.

Genitalia. Male: relatively small penis. Hypogonadism in terms of fertility (100 per cent) and testosterone production.

OCCASIONAL ABNORMALITIES. Seizures (less than 5 per cent); strabismus (33 per cent), nystagmus (15 per cent), keratoconus (6 per cent), cataract (1.3 per cent); low placement of ears; web neck; two ossification centers in manubrium sterni; funnel or pigeon breast; tracheoesophageal fistula, duodenal atresia; tetralogy of Fallot; incomplete fusion of vertebral arches of lower spine (37 per cent); only 11 ribs; cryptorchidism (27 per cent from birth to nine years and 14 per cent after 15 years); syndactyly of second and third toes. The incidence of leukemia is about 1:95, or close to 1 per cent. Thyroid disorders are more common, including athyreosis, simple goiter, and hyperthyroidism.

PRINCIPAL FEATURES IN NEWBORN. The diagnosis can generally be made shortly after birth, and therefore the following ten features of Down syndrome in the newborn are presented as set forth by Hall,[3] who found at least four of these abnormalities in all of 48 newborns with Down syndrome, and six or more in 89 per cent of them.

Hypotonia	80%
Poor Moro reflex	85%
Hyperflexibility of joints	80%
Excess skin on back of neck	80%
Flat facial profile	90%
Slanted palpebral fissures	80%
Anomalous auricles	60%
Dysplasia of pelvis	70%
Dysplasia of mid-phalanx of fifth finger	60%
Simian crease	45%

NATURAL HISTORY. Muscle tone tends to improve with age, whereas the rate of developmental progress slows with age. For example 23 per cent of a group of Down syndrome children under three years had a developmental quotient above 50, whereas none of those in the three to nine year group had intelligence quotients above 50. Though the I.Q. range is generally said to be 25 to 50 with an occasional individual above 50, the mean I.Q. for older patients is 24. Fortunately, social performance is usually beyond that expected for mental age, averaging three and one third years above mental age for the older individuals. Generally "good babies" and happy children, they tend toward mimicry, are friendly, have a good sense of rhythm, and enjoy music. Mischievousness and obstinacy may also be characteristics, and 13 per cent have serious emotional problems. Coordination is often poor, and the voice tends to be raucous.

Early developmental enrichment programs for Down syndrome children have resulted in improved rate of progress during the first four to five years of life. Whether such training programs will appreciably alter their ultimate level of performance remains to be determined.

Growth is relatively slow, and during the first eight years secondary centers of ossification are often late in development. However, during later childhood the osseous maturation is more "normal," and final height is usually attained around 15 years of age. Adolescent sexual development is usually somewhat less complete than normal. The girls may menstruate and can be fertile, whereas the males are considered infertile and have relatively low serum testosterone values.

The major cause for early mortality is congenital heart defects, and 44 per cent of those with cardiac anomalies die in infancy. Lower respiratory infections may pose a serious problem; however, between infancy and 40 years of age the mortality rate is not much greater than the normal. Low grade frequent problems are chronic rhinitis, conjunctivitis, and periodontal disease, none of which are easy to "cure."

ETIOLOGY. Trisomy for all or a large part of chromosome 21. The combined results of 11 unselected surveys totaling 784 cases showed the following relative frequencies of particular types of chromosomal alteration for Down syndrome:[4]

Full 21 trisomy	94%
21 Trisomy/normal mosaicism	2.4%
Translocation cases (with about equal occurrence of D/G and G/G translocations)	3.3%

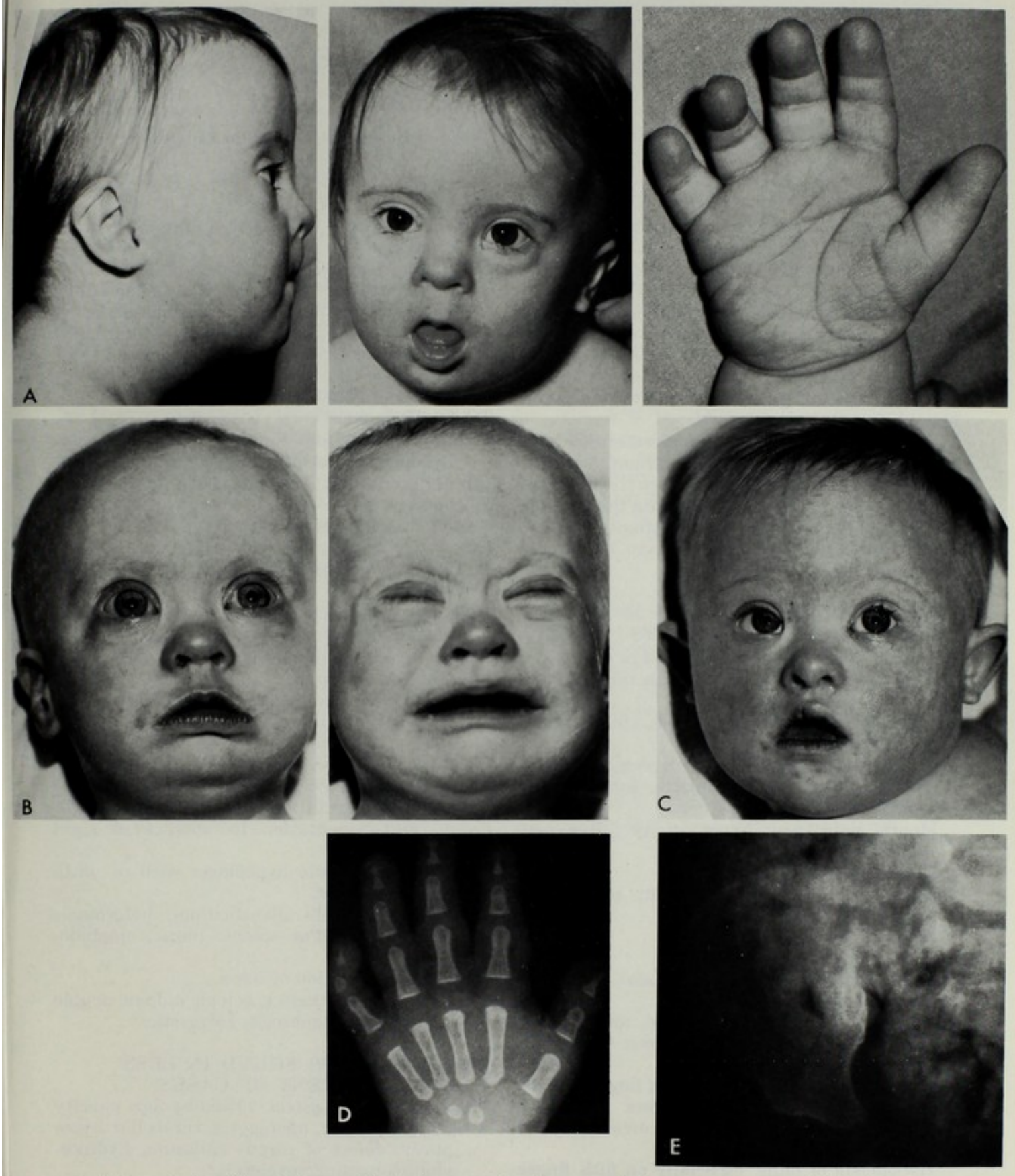
Faulty chromosome distribution leading to Down syndrome is more likely to occur at older maternal age, as shown in the following figures of incidence for Down syndrome for particular maternal ages: 15 to 29 years, 1 : 1500; 30 to 34 years, 1 : 800; 35 to 39 years, 1 : 270; 40 to 44 years, 1 : 100, and over 45 years, 1 : 50.

Though the general likelihood for *recurrence* of Down syndrome is 1 per cent, the principal problem in giving recurrence risk figures to parents is to first determine whether the Down syndrome child is a translocation case with a parent who is a translocation carrier and thereby has a relatively high risk for recurrence. The likelihood of finding a translocation in the Down syndrome child of a mother under 30 years of age is 6 per cent, and of such cases only one out of three will be found to have a translocation carrier parent. Therefore the estimated probability that either parent of a Down syndrome patient born of a mother under 30 years is a G/D or G/G translocation carrier is 2 per cent versus 0.3 per cent when the Down syndrome patient is born of a mother over 30 years of age. Having excluded a translocation carrier parent, the risk for recurrence may be stated as about 1 per cent. Though a low figure, it is enough to justify amniocentesis for chromosome studies on any future pregnancy, allowing for early termination of a 21 trisomy abortus. The recurrence risk for the rare translocation carrier parent will depend on the type of translocation and the sex of the parent.

REFERENCES

1. Down, J. L. H.: Observations on an ethnic classification of idiots. Clinical Lecture Reports, London Hospital, *3*:259, 1866.
2. Penrose, L. S., and Smith, G. F.: Down's Anomaly. Boston, Little, Brown & Co., 1966.
3. Smith, D. W., and Wilson, A. C.: The Child with Down's Syndrome. Philadelphia, W. B. Saunders Co., 1973.
4. Hall, B.: Mongolism in newborn infants. Clin. Pediatr. (Phila.), *5*:4, 1966.
5. Richards, B. W., Stewart, A., Sylvester, P. E., and Jasiewicz, V.: Cytogenetic survey of 225 patients diagnosed clinically as mongols. J. Ment. Defic. Res., *9*:245, 1965.

DOWN SYNDROME



A, Young infant. Flat facies, straight hair; protrusion of tongue; single crease on inturned fifth finger.

B and *C*, Inner canthal folds. Speckling of iris with lack of peripheral patterning. Small auricles, prominent at right. "Pouting" expression when crying. (From Smith, D. W.: J. Pediatr., *70*:474, 1967.)

D, Hypoplasia, mid-phalanx of fifth finger.

E, Shallow acetabular angle with small iliac wings having the shape of elephant ears.

TRISOMY 18 SYNDROME

Clenched Hand, Short Sternum, Low Arch Dermal Ridge Patterning on Fingertips

This condition was first recognized as a specific entity in 1960 by discovery of the extra 18 chromosome in babies with a particular pattern of malformation (Edwards et al.,[1] Patau et al.,[2] and Smith et al.[3]). It is the second most common multiple malformation syndrome, with an incidence of about 0.3 per 1000 newborn babies. There has been a 3:1 preponderance of females to males. Several good reviews set forth a full appraisal of this syndrome.[4-7]

More than 130 different abnormalities have been noted in the literature on patients with the 18 trisomy syndrome, and therefore the listing of abnormalities has been divided into those which occur in 50 per cent or more of patients, in 10 to 50 per cent of patients, and less than 10 per cent of patients.

ABNORMALITIES FOUND IN 50 PER CENT OR MORE OF PATIENTS

General. Feeble fetal activity, weak cry.
Altered, gestational timing; one third premature, one third postmature.
Polyhydramnios, small placenta, single umbilical artery.
Growth deficiency; mean birth weight, 2340 g.
Hypoplasia of skeletal muscle, subcutaneous and adipose tissue.
Mental deficiency, hypertonicity (after neonatal period).
Diminished response to sound.

Craniofacial. Prominent occiput, narrow bifrontal diameter.
Low set, malformed auricles.
Short palpebral fissures.
Small oral opening, narrow palatal arch.
Micrognathia.

Hands and Feet. Clenched hand, tendency for overlapping of index finger over third, fifth finger over fourth.
Absence of distal crease on fifth finger with or without third and fourth fingers.
Low arch dermal ridge pattern on six or more fingertips.
Hypoplasia of nails, especially on fifth finger and toes.
Short hallux, frequently dorsiflexed.

Thorax. Sternum short, with reduced number of ossification centers.
Small nipples.

Abdominal Wall. Inguinal or umbilical hernia and/or diastasis recti.

Pelvis and Hips. Small pelvis, limited hip abduction.

Genitalia. Cryptorchidism (male).

Skin. Redundancy, mild hirsutism of forehead and back, prominent cutis marmoratum.

Cardiac. Ventricular septal defect, auricular septal defect, patent ductus arteriosus.

ABNORMALITIES OCCURRING IN 10 TO 50 PER CENT OF CASES

Craniofacial. Wide fontanels, microcephaly, hypoplasia of orbital ridges.
Inner epicanthic folds, ptosis of eyelid, corneal opacity.
Cleft lip, cleft palate, or both

Hands and Feet. Ulnar or radial deviation of hand, hypoplastic to absent thumb, simian crease.
Equinovarus, rocker-bottom feet, syndactyly of second and third toes.

Thorax. Relatively broad, with or without widespread nipples.

Genitalia. Female: hypoplasia of labia major with prominent clitoris.

Anus. Malposed or funnel-shaped anus.

Cardiac. Bicuspid aortic and/or pulmonic valves, nodularity of valve leaflets, pulmonic stenosis, coarctation of aorta.

Lung. Malsegmentation to absence of right lung.

Diaphragm. Muscle hypoplasia with or without eventration.

Abdomen. Meckel's diverticulum, heterotopic pancreatic and/or splenic tissue, omphalocele.
Incomplete rotation of colon.

Renal. Horseshoe defect, ectopic kidney, double ureter, hydronephrosis, polycystic.

ABNORMALITIES FOUND IN LESS THAN 10 PER CENT OF CASES

Central Nervous System. Facial palsy, paucity of myelination, microgyria, cerebellar hypoplasia, defect of corpus callosum, hydrocephalus, meningomyelocele.

Craniofacial. Wormian cranial bones, shallow elongated sella. Slanted palpebral fissures, hypertelorism, colobomata of iris, cataract, microphthalmos, choanal atresia.

Hands. Syndactyly of third and fourth fingers, polydactyly, short fifth metacarpals, ectodactyly.

Other Skeletal. Radial aplasia. Incomplete ossification of clavicle. Hemivertebrae, fused vertebrae, short neck, scoliosis, rib anomaly, pectus, dislocated hip.

Genitalia. Male: hypospadias, bifid scrotum. Female: bifid uterus, ovarian hypoplasia.

Cardiovascular. Anomalous coronary artery, transposition, tetralogy of Fallot, coarctation of aorta, dextrocardia, aberrant subclavian artery, and intimal proliferation in arteries with arteriosclerotic change and medial calcification.

Abdominal. Pyloric stenosis, omphalocele, extrahepatic biliary atresia, hypoplastic gallbladder, gallstones, imperforate anus.

Renal. Hydronephrosis, polycystic (small cysts).

Endocrine. Thyroid or adrenal hypoplasia.

Other. Hemangiomata, thymic hypoplasia, tracheoesophageal fistula, thrombocytopenia.

NATURAL HISTORY. Babies with the 18 trisomy syndrome are usually feeble and have a limited capacity for survival. Resuscitation is often performed at birth, and they may have apneic episodes in the neonatal period. Poor sucking capability may necessitate nasogastric tube feeding, but even with optimal management they fail to thrive. Thirty per cent die within the first month and 50 per cent by two months; only 10 per cent survive the first year as severely mentally defective individuals. Once the diagnosis has been established, the author recommends limitation of all medical means for prolongation of life.

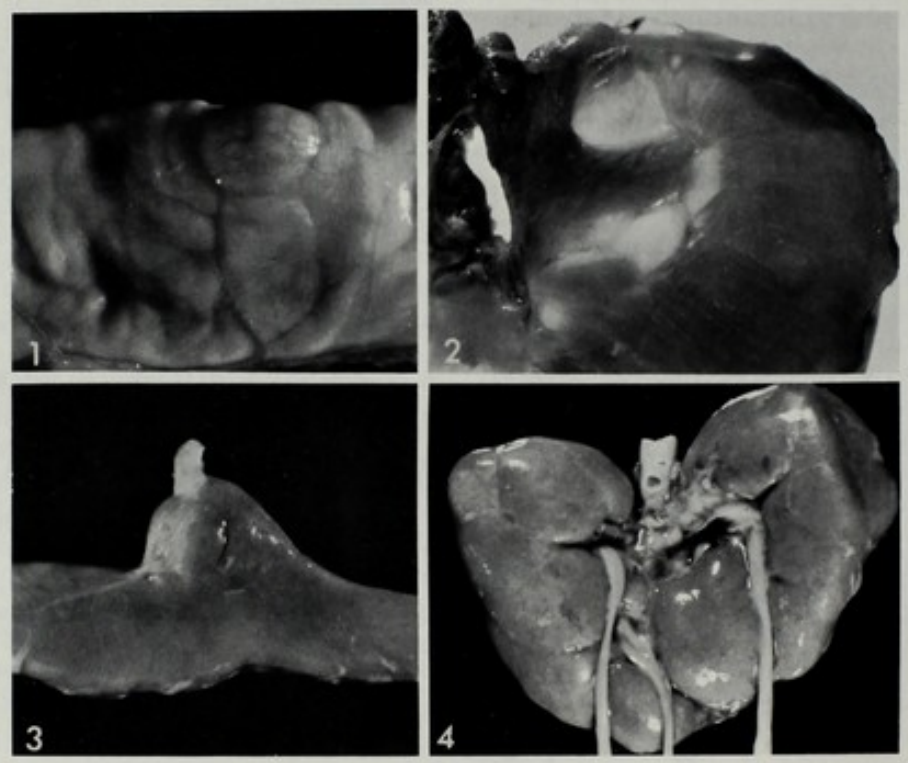
ETIOLOGY. Trisomy for all or a large part of the number 18 chromosome. The great majority of cases have full 18 trisomy, the result of faulty chromosomal distribution, which is most likely to occur at older maternal age; the mean maternal age at birth of babies with this syndrome is 32 years. Translocation cases, the result of chromosomal breakage, can only be excluded by chromosomal studies, and when such a case is found the parents should also have chromosomal studies to determine whether one of them is a balanced translocation carrier with high risk for recurrence in future offspring. Though no adequate studies or recurrence risk exist for full 18 trisomy cases, it seems safe to presume that the recurrence risk would be even lower than the 1 per cent for full 21 trisomy syndrome cases. This latter statement is predicated on the indication that most 18 trisomic individuals die in embryonic or fetal life, as suggested by the chromosomal findings in spontaneous abortuses.

REFERENCES

1. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., and Wolff, O. H.: A new trisomic syndrome. Lancet, *1*:787, 1960.
2. Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., and Wagnes, H. P.: Multiple congenital anomaly caused by an extra autosome. Lancet, *1*:790, 1960.
3. Smith, D. W., Patau, K., Therman, E., and Inhorn, S. L.: A new autosomal trisomy syndrome. J. Pediatr., *57*:338, 1960.
4. Smith, D. W.: Autosomal abnormalities. Am. J. Obstet. Gynecol., *90*:1055, 1964.
5. Taylor, A., and Polani, P. E.: Autosomal trisomy syndromes, excluding Down's. Guy's Hosp. Rep., *13*:231, 1964.
6. Butler, L. J., Snodgrass, A. J. A. I., France, N. E., Sinclair, L., and Russell, A.: No. E (16–18) trisomy syndrome: analysis of 13 cases. Arch. Dis. Child., *40*:600, 1965.
7. Warkany, J., Passarge, E., and Smith, L. B.: Congenital malformations in autosomal trisomy syndromes. Am. J. Dis. Child., *112*:502, 1966.
8. Weber, W. W.: Survival and the sex ratio in trisomy 17–18. Am. J. Hum. Genet., *19*:369, 1967.

TRISOMY 18 SYNDROME

Some Pathological Features



1. Ectopic pancreatic tissue in duodenum.
2. Meckel's diverticulum.
3. Defects of muscle development in diaphragm.
4. Horseshoe fused kidneys with extra ureter.



A, Note hypertonicity evident in clenched hands and crossed legs; short sternum (arrow marks lower end); narrow pelvis.

B, Prominent occiput; low-set, slanted auricle.

C, Clenched hand with index finger overlying third, hypoplasia of fifth fingernail, low arch dermal ridge configuration on fingertip, and dorsiflexed short hallux.

(From Smith, D. W.: Am. J. Obstet. Gynecol., *90*:1055, 1964.)

TRISOMY 13 SYNDROME

(D_1 Trisomy Syndrome)

Defects of Eye, Nose, Lip, and Forebrain of Holoprosencephaly Type; Polydactyly; Narrow Hyperconvex Fingernails; Skin Defects, Posterior Scalp

Apparently described by Bartholin in 1657,[1] this syndrome was not generally recognized until its trisomic etiology was discovered by Patau et al.[2] in 1960. The incidence is about one per 5000 births.

ABNORMALITIES FOUND IN 50 PER CENT OR MORE OF PATIENTS

Central Nervous System. Holoprosencephaly type defect with varying degrees of incomplete development of forebrain and olfactory and optic nerves.
Minor motor seizures, often with hypsarrhythmic EEG pattern.
Apneic spells in early infancy.
Severe mental defect.

Hearing. Apparent deafness (defects of organ of Corti in the two cases studied).

Cranium. Moderate microcephaly with sloping forehead.
Wide sagittal suture and fontanels.

Eyes. Microphthalmia, colobomata of iris, or both.
Retinal dysplasia, often including islands of cartilage.

Mouth. Cleft lip (60 to 80 per cent), cleft palate, or both.

Auricles. Abnormal helices with or without low set ears.

Skin. Capillary hemangiomata, especially forehead.
Localized scalp defects in parieto-occipital area.
Loose skin, posterior neck.

Hands and Feet. Distal palmar axial triradii.
Simian crease.
Hyperconvex narrow fingernails.
Flexion of fingers with or without overlapping and camptodactyly.
Polydactyly of hands and sometimes feet.
Posterior prominence of heel.

Other Skeletal. Thin posterior ribs with or without missing rib.
Hypoplasia of pelvis with shallow acetabular angle.

Cardiac. Abnormality in 80 per cent with ventricular septal defect, patent ductus arteriosus, auricular septal defect, and dextroposition, in decreasing order of frequency.

Genitalia. Male: cryptorchidism, abnormal scrotum.
Female: bicornuate uterus.

Hematological. Increased frequency of nuclear projections in neutrophils.
Unusual persistence of embryonic and/or fetal type hemoglobin.

Other. Single umbilical artery.
Inguinal or umbilical hernia.

ABNORMALITIES FOUND IN LESS THAN 50 PER CENT OF PATIENTS

Growth. Congenital hypoplasia, mean birth weight, 2480 g.

Central Nervous System. Hypertonia, hypotonia, agenesis of corpus callosum, hydrocephalus, fusion of basal ganglia, cerebellar hypoplasia, meningomyelocele.

Eyes. Shallow supraorbital ridges, slanting palpebral fissures, absent eyebrows, hypotelorism, hypertelorism, anophthalmos, cyclopia.

Nose, Mouth, and Mandible. Absent philtrum, narrow palate, cleft tongue, micrognathia.

Hands and Feet. Retroflexible thumb, ulnar deviation at wrist, low arch digital dermal ridge pattern, fibular S-shaped hallucal dermal ridge pattern, syndactyly, cleft between first and second toes, hypoplastic toenails, equinovarus, radial aplasia.

Cardiac. Anomalous venous return, overriding aorta, pulmonary stenosis, hypoplastic aorta, atretic mitral and/or aortic valves, bicuspid aortic valve.

Abdominal. Omphalocele, heterotopic pancreatic or splenic tissue, incomplete rotation of colon, Meckel's diverticulum.

Renal. Polycystic (31 per cent), hydronephrosis, horseshoe kidney, duplicated ureters.

Genitalia. Hypospadias, duplication and/or anomalous insertion of fallopian tubes, uterine cysts, hypoplastic ovaries.

Other. Thrombocytopenia, situs inversus of lungs, cysts of thymus, calcified pulmonary arterioles, large gallbladder, radial aplasia, flexion deformity of large joints, diaphragmatic defect.

NATURAL HISTORY. Forty-four per cent of these babies die within the first month and 69

per cent by six months; only 18 per cent survive the first year. Survivors have severe mental defects, often seizures, and fail to thrive. Only one adult, 33 years of age, has been detected. Because of the high infant mortality, surgical or orthopedic corrective procedures should be withheld in early infancy to await the outcome of the first few months. Furthermore, because of the severe brain defect, it is the opinion of the author that no medical means should be utilized to prolong the life of individuals with this syndrome, as should be self-evident from the accompanying illustrations.

ETIOLOGY. Trisomy for all or a large part of a specific D group (13–15) chromosome which is tentatively referred to as number 13. Older maternal age has been a factor in the occurrence of this aneuploidy syndrome, the mean maternal age being 30.9 years. Although no accurate empiric recurrence risk data are presently available, it is presumed that the likelihood for recurrence is of very low magnitude for the full 13 trisomy cases. As with Down syndrome, chromosomal studies are indicated on 13 trisomy syndrome babies born of young mothers, in order to detect the rare translocation patient having a balanced translocation parent for whom the risk for recurrence would be of major concern.

COMMENT. The defects of midface, eye, and forebrain, which occur in variable degree as a feature of this syndrome, appear to be the consequence of a single defect in the early (three weeks) development of the prechordal mesoderm, which is not only necessary for morphogenesis of the midface but also exerts an inductive role on the subsequent development of the prosencephalon, the forepart of the brain. This type of defect has been referred to as holoprosencephaly or arhinencephaly and varies in severity from cyclopia, to cebocephaly, to less severe forms.

REFERENCES

1. Warburg, M., and Mikkelsen, M.: A case of 13-15 trisomy or Bartholin-Patau's syndrome. Acta Ophthalmol. (Kbh.), *41*:321, 1963.
2. Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., and Wagner, H. P.: Multiple congenital anomaly caused by an extra chromosome. Lancet, *1*:790, 1960.
3. Smith, D. W.: Autosomal abnormalities. Am. J. Obstet. Gynecol., *90*:1055, 1964.
4. Warkany, J., Passarge, E., and Smith, L. B.: Congenital malformations in autosomal trisomy syndromes. Am. J. Dis. Child., *112*:502, 1966.

TRISOMY 13 SYNDROME

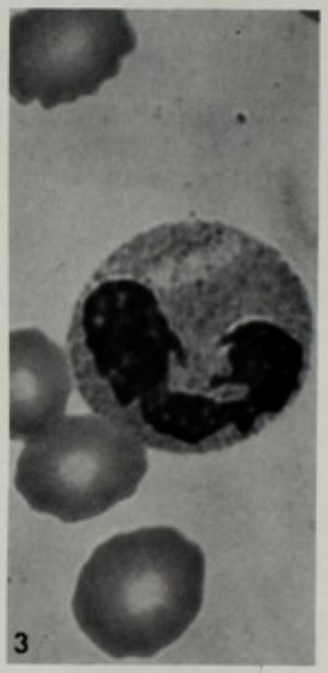


Trisomy 13 patient at six weeks (22 inches, 9 pounds) and again at two years (30 inches, 15 pounds).

Some Pathological Features







1. Lack of septation of forebrain (holoprosencephaly).
2. Dysplastic retina with rosette formation.
3. Excess nuclear projections in polymorphonuclear leukocyte.



A, Note sloping forehead, variable defect in facial development. (From Smith, D. W., et al.: J. Pediatr., *62*:326, 1963.)

B, Narrow hyperconvex fingernails, anomalous scrotum, prominent heel, and posterior scalp lesions. (From Smith, D. W.: Am. J. Obstet. Gynecol., *90*:1055, 1964.)

TRISOMY 8 SYNDROME

Thick Lips, Deep-Set Eyes, Prominent Ears, Camptodactyly

Patients with trisomy for a C-group autosome have been recognized since 1963.[1] Most of them have been mosaics of trisomy C/normal. The phenotype tends to be similar and more recently chromosomal banding techniques have identified the extra chromosome as number 8. About 30 cases have been reported.

ABNORMALITIES

Growth. Mild to moderate growth deficiency.

Performance. Mild to severe mental deficiency with tendency to poor coordination.

Craniofacial. Tendency toward prominent forehead, deep-set eyes, strabismus, hypertelorism with broad nasal root and prominent nares, full lips, micrognathia, high arched palate, and prominent cupped ears with thick helices.

Limbs. Camptodactyly of second through fifth fingers and toes, limited elbow supination.

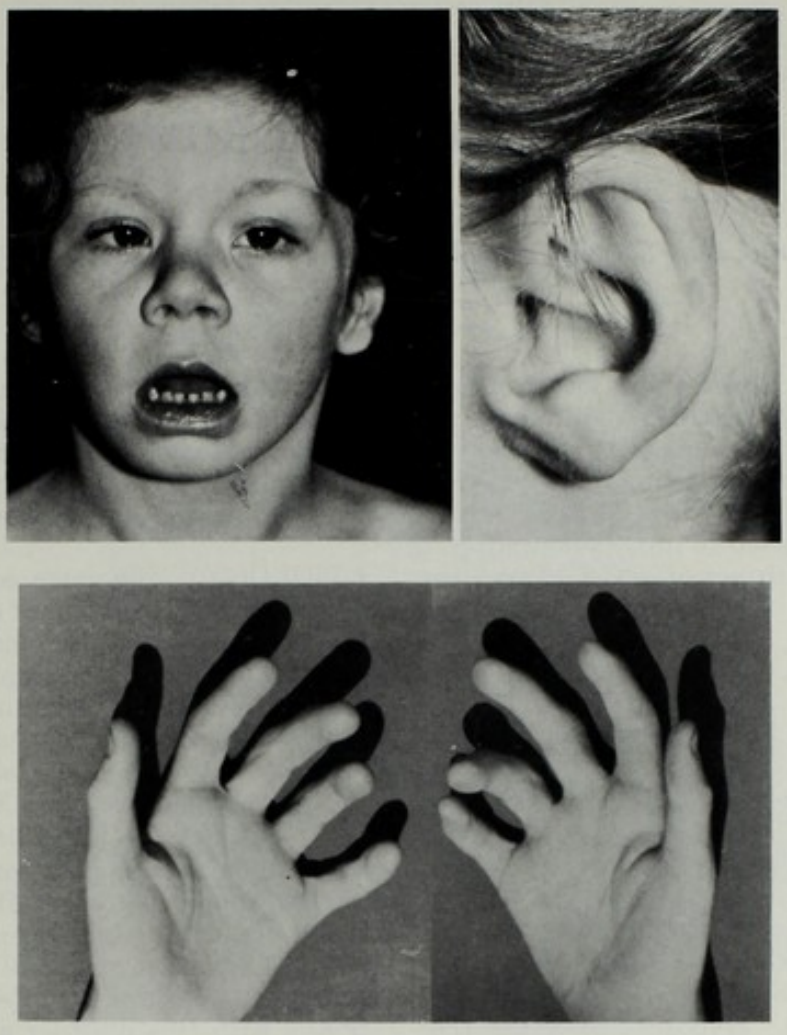
OCCASIONAL OR UNCERTAIN INCIDENCE. Absent patellae, conductive deafness, vertebral anomaly (bifid vertebrae, extra lumbar vertebra, spina bifida occulta), cryptorchidism, agenesis of corpus callosum. Hypoplastic anemia, leukopenia.

NATURAL HISTORY. The natural history is largely dependent on the severity of mental deficiency which is probably related to the proportion of trisomy 8 versus normal cells.

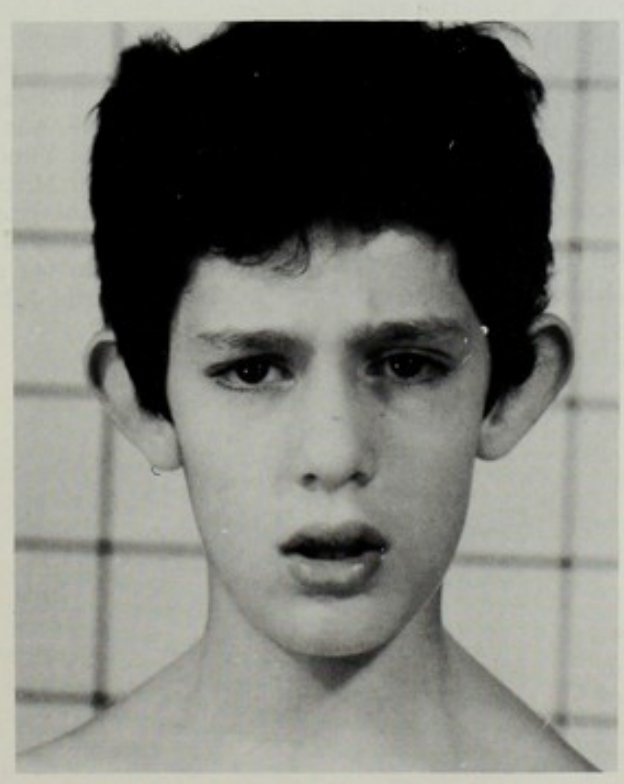
ETIOLOGY. Trisomy 8, the majority of patients being mosaics. Apparently full trisomy 8 is usually an early lethal.

REFERENCES

1. Stalder, G. R., Buhler, E. M., and Weber, J. R.: Possible trisomy in chromosome group 6–12. Lancet, *1*:1379, 1963.
2. Lejeune, J., et al.: Sur trois cas de trisomie C. Ann. Genet. (Paris), *12*:28, 1969.
3. Bijlsma, J. B., Wijffels, J. C. H. M., and Tegelaers, W. H. H.: C8 trisomy mosaicism syndrome. Helv. Paediatr. Acta, *27*:281, 1972.
4. Riccardi, V. M., Atkins, L., and Holmes, L. B.: Absent patellae, mild mental retardation, skeletal and genitourinary anomalies, and group C autosomal mosaicism. J. Pediatr., *77*:664, 1970.
5. Caspersson, T., Lindsten, J., Zech, L., Buckton, K. E., and Price, W. H.: Four patients with trisomy 8 identified by the fluorescence and giemsa banding techniques. J. Med. Genet., *9*:1, 1972.



Above, Boy with trisomy 8/normal mosaicism. (From Riccardi, V. M., et al.: J. Pediatr. *77*:664, 1970.)
Below, Ten year old mentally deficient with trisomy 8/normal mosaicism. Note the prominent ears. (From De Grouchy, J., et al.: Ann. Genet. (Paris), *14*:69, 1971.)



TRIPLOIDY SYNDROME

Large Placenta, Low-Set Malformed Ears, Syndactyly of Third and Fourth Fingers

Triploidy, with a full extra set of chromosomes, is estimated to occur in about 1 per cent of conceptuses. The vast majority are expelled early in pregnancy, being a frequent occurrence among spontaneous abortuses. Only about 15 cases have been reported in infants born after 28 weeks gestation, with seven being of full-term gestation.

ABNORMALITIES. Noted in 50 per cent or more of cases.

Placenta. Large with tendency toward hydatidiform changes.

Growth. Variable prenatal growth deficiency.

Craniofacial. Large posterior fontanel. Microphthalmia, coloboma of iris, low-set malformed ears.

Limb. Syndactyly of third and fourth fingers, simian crease, talipes equinovarus.

Heart. Congenital heart defect.

Genitalia (in males). Hypospadias, cryptorchidism, Leydig cell hyperplasia.

Other. Brain anomalies including hydrocephalus, adrenal hypoplasia, cystic renal dysplasia. Toxemia during pregnancy.

OCCASIONAL ABNORMALITIES. Noted in less than 50 per cent of cases. Hypertelorism, low nasal bridge, aberrant skull shape, cleft lip and/or palate, micrognathia. Proximal placement of thumbs. Lumbosacral meningomyelocele. Micropenis, bifid scrotum, ovarian hypoplasia. Hydronephrosis. Incomplete rotation of colon.

NATURAL HISTORY. All cases of full triploidy have either been stillborn or died in the early neonatal period, the average postnatal survival being about 20 hours. Diploid/triploid mosaic individuals, who may have many of the features of full triploidy, may survive. They have had moderate to severe mental deficiency.

ETIOLOGY. The extra set of chromosomes is believed to be the result of double fertilization of the ovum (diandry) in some cases and failure of the ovum to exclude a polar body (digyny) in other cases. About two thirds of the cases have been XXY, the majority of whom have incomplete development of the external genitalia, and the remainder have been XXX. Older maternal age has not been a factor and there is no data to indicate an increased recurrence risk. The mother should be told that she must be exceptional at carrying babies and the parents should be told that they may well have an exceptional genetic background in order to have had a conceptus with this disorder survive to late gestation. Thus the situation is best interpreted as a late miscarriage.

REFERENCES

1. Bernard, R., Stahl, A., Coignet, J., Giraud, F., Hartung, M., Brusquet, Y., and Passeron, P.: Triploidie chromosomique chez un nouveau-né polymalformé. Ann. Genet. (Paris), *10*:70, 1967.
2. Edwards, J. H., Yuncken, C., Rushton, D. I., Richards, S., and Mittwoch, U.: Three cases of triploidy in man. Cytogenetics, *6*:81, 1967.
3. Walker, S., Andrews, J., Gregson, N. M., and Gault, W.: Three further cases of triploidy in man surviving to birth. J. Med. Genet., *10*:135, 1973.



Prematurely stillborn baby. Note low-set small ear, low nasal bridge, micrognatnia, loose skin at neck, partial syndactyly of third and fourth fingers, and simian creases.

4p– Syndrome

(Chromosome Number 4 Short Arm Deletion Syndrome)

Ocular Hypertelorism with Broad or Beaked Nose, Microcephaly and/or Cranial Asymmetry, and Low-Set, Simple Ear with Preauricular Dimple

After delineation of the cri-du-chat syndrome, occasional patients with deletions of the short arm of a B-group chromosome were found who lacked the typical cry and some other features of that condition. Autoradiographic labeling studies revealed that the deficient chromosome was a number 4 rather than a number 5, and the detection of further cases with consistent clinical findings have allowed the definition of the syndrome.

ABNORMALITIES (12 cases)

Growth. Marked growth deficiency, prenatal onset. Microcephaly.

Performance. Feeble fetal activity. Hypotonia. Severe mental deficiency; seizures.

Craniofacial. Strabismus, iris deformity, ocular hypertelorism, epicanthic folds; prominent glabella, cleft lip and/or palate, downturned "fishlike" mouth, short upper lip and philtrum, and micrognathia. Posterior midline scalp defects. Cranial asymmetry. Preauricular tag or pit.

Extremities. Hypoplastic dermal ridges, low dermal ridge count. Simian creases. Talipes equinovarus.

Other. Hypospadias, cryptorchidism, sacral dimple or sinus. Cardiac anomaly.

OCCASIONAL ABNORMALITIES. Exophthalmos, defect of the medial half of the eyebrows, cardiac defect, metatarsus equinovarus, absence of pubic rami, delayed bone age, precocious puberty.

NATURAL HISTORY. These children are profoundly mentally defective and tend to have severe grand mal and minor motor seizures. Those who survive beyond early childhood have shown continued slow growth, with a propensity for respiratory infections.

ETIOLOGY. Partial deletion of the short arm of chromosome 4. The parents' chromosomes should be studied to determine whether either is a translocation carrier parent, which is seldom the case.

COMMENT. Although chromosome analysis may be misleading because of difficulties in discriminating between chromosomes number 4 and 5, this condition can be distinguished from the cri-du-chat syndrome on clinical grounds.

REFERENCES

1. Leao, J. C., et al.: New syndrome associated with partial deletion of short arms of chromosome no. 4. J.A.M.A., *202*:434, 1967.
2. Pfeiffer, R. A.: Neue Dokumentation zur Abgrenzung eines Syndroms der Deletion des kurzen Arms eines Chromosoms Nr. 4. Z. Kinderheilkd., *102*:49, 1968.
3. Wolf, U., and Reinwein, H.: Klinische und cytogenetische Differentialdiagnose de Defizienzen an den kurzen Armen der B-Chromosomen. Z. Kinderheilkd., *98*:235, 1967.
4. Guthrie, R. D., et al.: The 4p– syndrome. Am. J. Dis. Child., *122*:421, 1971.





A to *C*, Two week old, 11 month old, and two and three fourths year old. (From Wolf, U., and Reinwein, H.: Z. Kinderheilkd., *98*:235, 1967.)

D, Five and three fourths year old with height age of ten months, and intelligence quotient of less than 20.

E, Seven year old with height age of three and one half years; performance age of less than six months.

F, Relatively simple form of ear with cutaneous pit.

G, B group of chromosomes from patient shown in *E*.

CRI-DU-CHAT SYNDROME

(Partial Deletion of the Short Arm of Chromosome Number 5 Syndrome)

Cat-Like Cry in Infancy, Microcephaly, Downward Slant of the Palpebral Fissures

Lejeune et al.[1] first described this condition in 1963. Further reports have raised to about 30 the number of cases described.

ABNORMALITIES

General. Low birth weight (less than 2.5 kg)	72%
Slow growth	100%
Cat-like cry	100%
Performance. Mental deficiency	100%
Hypotonia	78%
Craniofacial. Microcephaly	100%
Round face	68%
Hypertelorism	94%
Epicanthic folds	85%
Downward slanting of the palpebral fissures	81%
Strabismus, often divergent	61%
Low-set and/or poorly formed ears	58%
Facial asymmetry	
Heart. Congenital heart disease (variable in type)	30%
Hands. Simian crease	81%
Distal axial triradius	40%
Mildly short metacarpals	

OCCASIONAL ABNORMALITIES. Cleft lip and cleft palate, myopia, optic atrophy, preauricular skin tag, bifid uvula, dental malocclusion, short neck, clinodactyly, inguinal hernia, cryptorchidism, absent kidney and spleen, and hemivertebra, scoliosis, flat feet, and premature graying of hair.

NATURAL HISTORY. Birth weight has ranged from 1600 to 3570 grams with a mean of 2650 grams. As babies they tend to be unusually squirmy in their activity. The mewing cry, ascribed to abnormal laryngeal development, becomes less pronounced with increasing age of the patient, thus making the diagnosis more difficult in older patients. The I.Q. is most commonly in the 20 to 30 range. The majority become ambulatory; however, only one patient has developed limited speech. Scoliosis is a frequent occurrence.

ETIOLOGY. The underlying chromosomal aberration, partial deletion of the short arm of chromosome number 5, has appeared as a fresh phenomenon in the majority of the cases. A balanced translocation parent, with an increased risk for recurrence, has been found in 10 to 15 per cent of the cases.

REFERENCES

1. Lejeune, J., Lafourcade, J., Berger, R., Vialatte, J., Boeswillwald, M., Seringe, P., and Turpin, R.: Trois cas de délétion partielle du bras court du chromosome 5. C. R. Acad. Sci. [D] (Paris), *257*:3098, 1963.
2. Berg, J. M., Delhanty, J. D. A., Faunch, J. A., and Ridler, M. A. C.: Partial deletion of short arm of a chromosome of the 4 and 5 group (Denver) in an adult male. J. Ment. Defic. Res., *9*:219, 1965.
3. Breg, W. R., et al.: The Cri-du-chat syndrome in adolescents and adults. J. Pediatr., *77*:782, 1970.



A, Nine month old with height age of 5 months; birth length 18 inches. Note the delay in dentition.

B, Three and five sixths year old, height age of one and one half years. Note the inner epicanthal fold and relatively small cranium with narrow forehead.

(From Smith, D. W.: J. Pediatr., *70*:475, 1967.)

13q– SYNDROME

Microcephaly with High Nasal Bridge, Eye Defect, Thumb Hypoplasia

Partial deletion of the long arm of one of the D group chromosomes was initially reported in 1963 by Lele, et al.[1] in a mentally deficient and growth deficient patient with retinoblastoma. Subsequently at least 11 cases have been recorded and the deleted chromosome has been considered to be number 13. The phenotype has been variable, but a pattern of malformation is emerging which should allow for suspicion of this disorder. A similar phenotype has been noted in 13 ring chromosome patients, who are missing part of the short arm as well as part of the long arm of chromosome 13. The following features are those found in 13q– patients.

ABNORMALITIES. Other than mental and growth deficiency, the particular anomalies have occurred in only one third to two thirds of the cases.

Growth. Growth deficiency, usually of prenatal onset.

CNS. Mental deficiency. Microcephaly with tendency toward trigonocephaly- and holoprosencephaly-type of brain defects.

Facial. Prominent nasal bridge, hypertelorism. Ptosis, epicanthus, microphthalmia, coloboma. Retinoblastoma, usually bilateral. Prominent maxilla, micrognathia. Prominent ears, slanting, low placement.

Neck. Short, webbing.

Limbs. Small to absent thumbs, clinodactyly of fifth finger. Talipes equinovarus, short big toe.

Cardiac. Cardiac defect.

Genitalia. Hypospadias, cryptorchidism.

OCCASIONAL ABNORMALITIES. Found in one or two of the 11 patients. Facial asymmetry, narrow palate, imperforate anus, bifid scrotum, pelvic anomaly, renal anomaly.

NATURAL HISTORY. Though the degree of mental deficiency has been variable, most patients have been severely retarded. The oldest, a 25 year old, was unable to speak or ambulate.

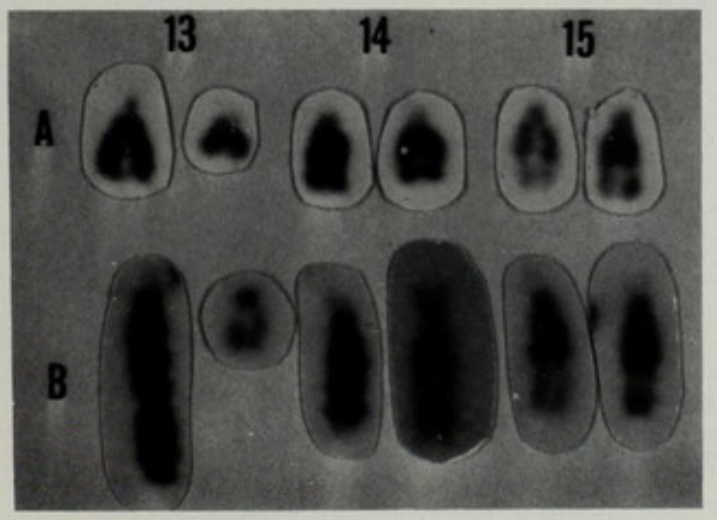
ETIOLOGY. Deletion of part of the long arm of a 13 chromosome. Ring 13 chromosome individuals may have a similar pattern of malformation.

COMMENT. The finding of retinoblastoma in at least three 13q– patients as well as several with the 13 ring chromosome indicates a significant causal relationship between this genetic imbalance and the likelihood of developing this type of tumor. Chromosome studies would seem merited in patients with retinoblastoma who also have mental and growth deficiency, plus or minus some of the foregoing anomalies.

REFERENCES

1. Lele, K. P., Penrose, L. S., and Stallarf, H. B.: Chromosome deletion in a case of retinoblastoma. Ann. Hum. Genet., *27*:171, 1963.
2. Allerdice, P. W., Davis, J. G., Miller, O. J., Klinger, H. P., Warburton, D., Miller, D. A., Allen, F. H., Jr., Abrams, C. A. L., and McGilvray, E.: The 13q– deletion syndrome. Am. J. Hum. Genet., *21*:499, 1969.
3. Taylor, A. I.: Dq–, Dr and retinoblastoma. Humangenetik, *10*:209, 1970.





Above, Patient, who died at three months, with microcephaly, cleft palate, low-set ears, short neck with slight webbing, relatively short limbs with clenched hands, short sternum, and marked cutis marmoratum. *Left,* D group chromosomes showing 13q− deletion in the patient (*A*) and her mother (*B*), who is a 13/13 balanced translocation carrier. (Courtesy of Dr. M. Jansch, St. Joseph's Hospital, Fort Wayne, Indiana.)

18p– SYNDROME

Mental and Growth Deficiency, Ptosis or Epicanthal Folds, Prominent Auricles

Deletion of the short arm of chromosome 18 was first noted by de Grouchy, et al. in 1963.[1] Subsequently more than 75 cases have been reported. There is rather broad variability in the phenotype.

ABNORMALITIES.[1–4] The most consistent features:

Growth. Mild to moderate growth deficiency.

CNS. Mental deficiency, tendency toward hypotonia. Microcephaly (mild).

Facial. Ptosis of eyelid(s), epicanthal folds, low nasal bridge, hypertelorism, rounded facies, micrognathia, wide mouth, downturning corners at mouth, large protruding ears.

Dental. High frequency of caries.

Limb. Relatively small hands and feet.

Other. Pectus excavatum.

OCCASIONAL OR UNCERTAIN INCIDENCE

Immunological. IgA absence or deficiency (9/19), usually asymptomatic.

CNS and Facial. Holoprosencephaly-arhinencephaly-type defect (five cases).

Skin and Hair. Alopecia (three cases), hypopigmentation.

Other. Cataract, strabismus, web neck, broad chest, kyphoscoliosis, clinodactyly of fifth fingers, simian crease, cubitus valgus, inguinal hernia, dislocation of hip, talipes equinovarus.

Development of rheumatoid arthritis-like signs and symptoms.

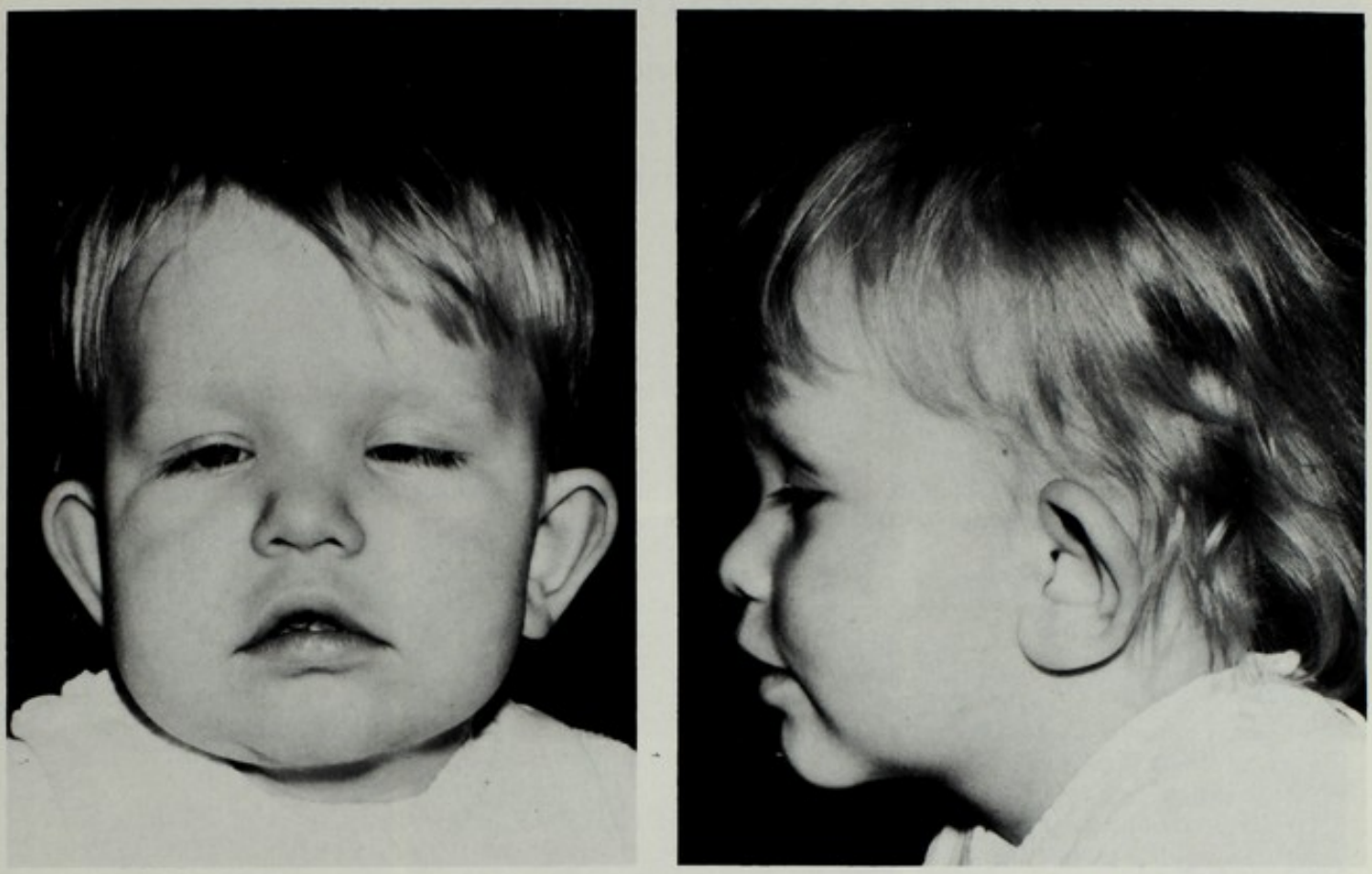
NATURAL HISTORY. Mild to severe mental deficiency: I.Q.'s range from 25 to 75 with an average of about 45 to 50. There is a dissociation between language ability and practical performance; many do not speak even simple sentences before seven to nine years of age. Restlessness, emotional lability, fear of strangers, and lack of concentration capability are frequent features in their behavior. They can best be helped in small groups for the mentally deficient. The prognosis is poor for those patients with holoprosencephaly-type defect. Otherwise, life expectancy does not seem to be impaired. Alopecia, when a problem, has developed during infancy. Adequate adaptation has occurred for some patients, who can be reproductive.

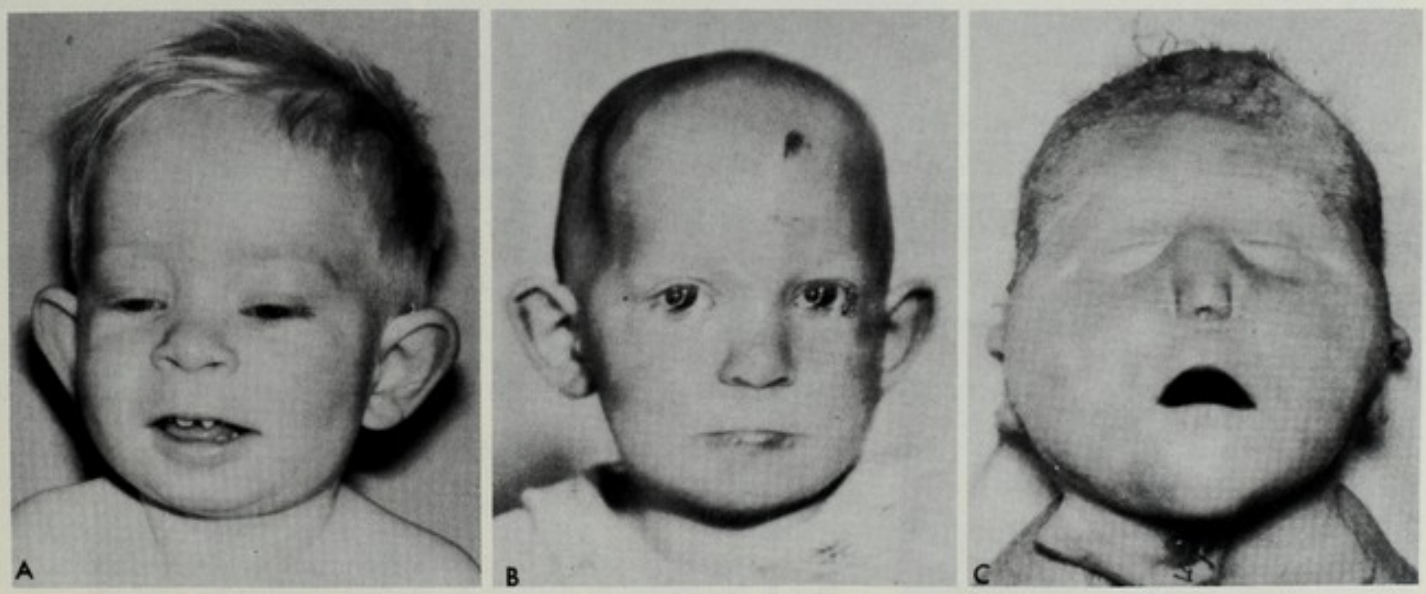
ETIOLOGY. Short-arm 18 deletion, sometimes as part of the deficiency in a ring-18 chromosome. Parents should be studied to determine whether either is a balanced translocation carrier or has the unbalanced 18p– deletion. Affected offspring have occurred from a parent with the same deletion, who would presumably have a 50 per cent risk.

There has been a 60 per cent predominance of affected females. The mean parental ages of 31.3 years for the mothers and 35.7 for the fathers are older than average.

REFERENCES

1. De Grouchy, J., Lamy, M., Thieffry, S., Arthuis, M., and Salmon, C.: Dysmorphie complexe avec oligophrénie: Délétion des bras courts d'un chromosome 17–18. C. R. Acad. Sci. [D] (Paris), *256*:1028, 1963.
2. Uchida, I. A., McRae, K. N., Want, H. C., and Ray, M.: Familial short arm deficiency of chromosome 18 concomitant with arrhinencephaly and alopecia congenita. Am. J. Hum. Genet., *17*:410, 1965.
3. Reinwein, H., Struwe, F. E., Bettecken, F., and Wolf, U.: Defizienz am kurzen Arm eines Chromosoms Nr. 18 (46,XX,18p–). Ein einheitliches Missbildungs. syndrom. Monatsschr. Kinderheilkd., *116*:511, 1968.
4. Schinzel, A., Schmid, U., Lüscher, U., Nater, M., Brook, C., and Steinmann, B.: The 18p– syndrome. Archiv für Genetik, in press.





Above, Three year old. (From Reinwein, H., et al.: Monatsschr. Kinderheilkd., *116*:511, 1968.)

Below, Mother (mosaic 18p−/normal) shown as a child (*B*) and two of her affected offspring (*A* and *C*), showing variability in expression for the same inherited 18p− deletion, including alopecia (*B*) and cebocephaly (*C*). (From Uchida, I. A., et al.: Am. J. Hum. Genet., *17*:410, 1965.)

18q– SYNDROME

(Long Arm 18 Deletion Syndrome)

Midfacial Hypoplasia, Prominent Antihelix, Whorl Digital Pattern

Discovered by de Grouchy, et al. in 1964, this genetic imbalance syndrome has been documented in more than 29 cases.

ABNORMALITIES

Growth. Small stature.

Performance. Mental deficiency with hypotonia, poor coordination, nystagmus, conductive deafness.

Craniofacial. Microcephaly.
Midfacial hypoplasia with deep set eyes.
Carp-shaped mouth, narrow palate.

Ears. Prominent antihelix, antitragus, or both.
Narrow or atretric external canal.

Limbs. Long hands, tapering fingers and short first metacarpal with proximal thumb.
High frequency whorl digital pattern, distal axial triradius, simian crease.
Abnormal toe placement.
Vertical talus with or without talipes equinovarus.

Genitalia. Female: hypoplastic labia minora.
Male: cryptorchidism with or without small scrotum and penis.

Other. Skin dimples over acromion, knuckles.
Cardiac defect.

OCCASIONAL ABNORMALITIES

Eye. Inner epicanthic folds, slanted palpebral fissures, ocular hypertelorism, microphthalmia, corneal abnormality, cataract, retinal defect, abnormal optic disc.

Ear. Atretic middle ear, low-set ears.

Other. Cleft palate (30 per cent), widely spaced nipples, extra rib, horseshoe kidney, lipomata at lateral border of feet. Eczema. Absence of IgA globulin.

NATURAL HISTORY. Mental deficiency, with I.Q.'s from 40 to 85, and growth deficiency, coupled with variable visual and hearing problems, may leave these individuals seriously handicapped. However, some patients with this deletion have not been severely affected. For example, a ten year old child studied by Wertelecki was not obviously debilitated.

ETIOLOGY. Deletion of part of the long arm of chromosome 18; most commonly a simple deletion and occasionally as a part of a ring chromosome 18.

REFERENCES

1. De Grouchy, J., Royer, P., Salmon, C., and Lamy, M.: Délétion partielle du bras long du chromosome 18. Path. Biol. (Paris), *12*:579, 1964.
2. Wertelecki, W., and Gerald, P. S.: Clinical and chromosomal studies of the 18q– syndrome. J. Pediatr., *78*:44, 1971.





A, Young infant. Note shape of mouth, midfacial hypoplasia, and prominent antihelix. (Courtesy of E. Engel, Vanderbilt University.)

B, Infant. Note prominent antihelix and absence of external auditory canal openings.

C, Note mild slant to palpebral fissures, strabismus, and facial asymmetry.

D, Note mouth and micrognathia.

E, Note prominent forehead in relation to hypoplasia of midface.

(*B* to *E* courtesy of W. Wertelecki, National Cancer Institute–NIH, P. S. Gerald, Boston Children's Hospital.)

21q– SYNDROME

(Antimongolism Syndrome, Long Arm 21 Deletion Syndrome)

Downslanting Palpebral Fissure, Large Malformed External Ears, Micrognathia

One other case has been reported since Lejeune, et al.[1] described this condition in 1964,[2] and a third case has been studied by German.[3]

ABNORMALITIES

Growth. Birth weight below 2.5 kg.

Performance. Apparent mental deficiency and hypertonia.

Facies. Blepharochalasis (redundant eyelids), broad nasal bridge, antimongoloid slanting of the palpebral fissures, prominent nasal bridge, large external ear with wide external auditory canal, and micrognathia.

Hands. Dysplastic nails, distal axial triradii.

Other. Hypospadias, pyloric stenosis, thrombocytopenia, retarded osseous maturation.

OCCASIONAL ABNORMALITIES. Seizures; cataracts; absent helix, preauricular tags; cryptorchidism; agenesis of the left kidney; inguinal hernia; hemivertebrae; syndactyly; increased iliac index; eosinophilia; increased leukocyte alkaline phosphatase.

NATURAL HISTORY. Usually severe mental, and moderate to severe growth deficiency.

ETIOLOGY. The partial deletion of the long arm of the 21 chromosome has been of different extent in each of the cases, which may account for some of the variability in phenotypic expression. Other cases have been mosaics with a 21 monosomy/normal cell admixture.

REFERENCES

1. Lejeune, J., Berger, R., Réthoré, M., Archambault, L., Jerome, H., Thieffry, S., Aicardi, J., Broyer, M., Lafourcade, J., Cruveiller, J., and Turpin, R.: Monosomie partielle pour un petit acrocentrique. C. R. Acad. Sci. [D] (Paris), *259*:4187, 1964.
2. Reisman, L. E.: Anti-mongolism. Studies in an infant with a partial monosomy of the 21 chromosome. Lancet, *1*:394, 1966.
3. Greenwood, R. D., and Sommer, A.: Monosomy G: Case report and review of the literature. J. Med. Genet., *8*:496, 1971.



Four day old. Note large ears, micrognathia, and malar hypoplasia with downslanting palpebral fissures. (From Reisman, L. E.: Lancet, *1*:394, 1966.)

COLOBOMA OF IRIS–ANAL ATRESIA SYNDROME

(Cat-Eye Syndrome)

Coloboma of Iris, Downslanting Palpebral Fissures, Anal Atresia

This pattern of malformation and its chromosomal etiology were discovered by Schmid in Zurich and Fraccaro in Pavia, and the condition was briefly reported by Schachenmann et al.[1] in 1965. More than 16 cases have been reported.

ABNORMALITIES

Growth. Variable growth deficiency.

Performance. Mild to moderate mental deficiency.

Facies. Colobomata of iris (lower vertical).
Mild hypertelorism and slight downward slant to palpebral fissures, epicanthic folds.
Preauricular fistula, skin tag.

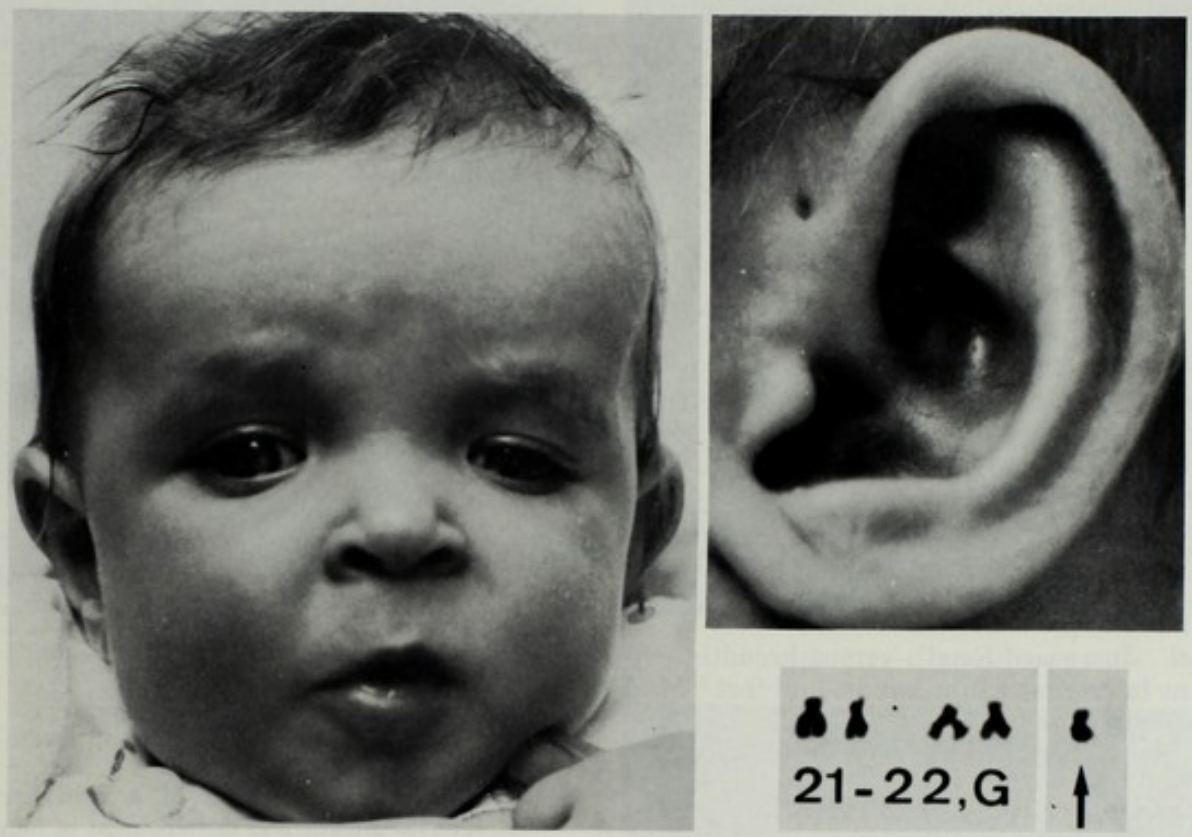
Intestine. Anal atresia with rectovestibular fistula.

OCCASIONAL ABNORMALITIES. Microphthalmos, low-set malformed ears, cardiac defect, dislocation of hip, unilateral renal aplasia.

ETIOLOGY. An abnormally small acrocentric extra chromosome, about half the size of a G group autosome. Bühler[4] considers this extra chromosome to most likely be a deleted number 22. Reproduction has occurred in this disorder allowing for a dominant mode of inheritance.

REFERENCES

1. Schachenmann, G., Schmid, W., Fraccaro, M., Mannini, A., Tiepolo, L., Perona, G. P., and Sartori, E.: Chromosomes in coloboma and anal atresia. Lancet, *2*:290, 1965.
2. Schmid, W.: Pericentric inversions (report of two malformation cases suggestive of parental inversion heterozygosity). J. Genet. Hum., *16*:89, 1967.
3. Fryns, J. P., Eggermont, E., Verresen, H., and van den Berghe, H.: A newborn with the cat-eye syndrome. Humangenetik, *15*:242, 1972.
4. Bühler, E. M., Méhes, K., Müller, H., and Staller, G. R.: Cat-eye syndrome, a partial trisomy 22. Humangenetik, *15*:150, 1972.



Infant showing downslanting palpebral fissures, colobomata of iris, and preauricular pits. Arrow denotes extra chromosome. (From Schmid, W.: J. Genet. Hum., *16*:89, 1967.)

XYY SYNDROME

Tall Stature, Aberrant Behavior

Despite an incidence of one in 840 newborn males, the XYY individual is seldom detected during childhood, or even in the adult. The features of the XYY syndrome are often subtle and not overtly suggestive of a chromosomal abnormality disorder. However, a pattern of variable abnormalities has come to be appreciated, which may allow for clinical suspicion of the XYY syndrome in childhood.[1-7]

ABNORMALITIES. Variable features from among the following:

Growth. Acceleration in midchildhood.

Performance. Dull mentality. Explosive behavior, sometimes antisocial.

Relative weakness with poor fine motor coordination and sometimes a fine intentional tremor.

Dentition. Large teeth.

Facies. Prominent glabella, asymmetry, long ears.

Skeletal. Increased length versus breadth; evident in cranial vault, hands, and feet.[2] Mild pectus excavatum.

Skin. Severe nodulocystic acne at adolescence.

OCCASIONAL ABNORMALITIES

Skeletal. Radioulnar synostosis.

Genital. Cryptorchidism, small penis, hypospadias.

Other. EEG abnormality. EKG showing prolonged PR interval.

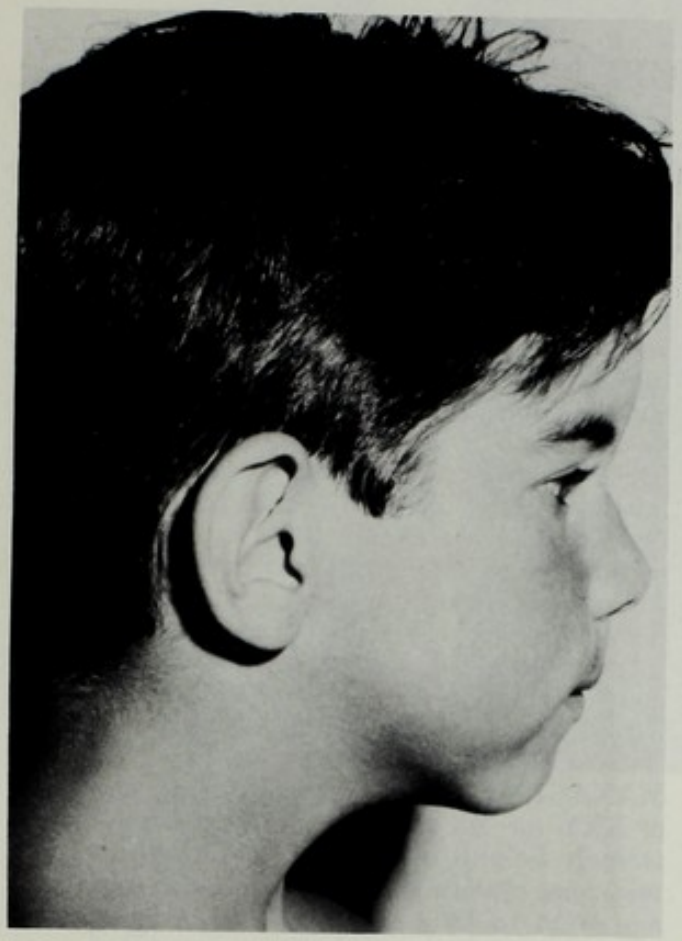
NATURAL HISTORY. Though occasionally long at birth, the tendency toward tall stature is usually not evident until five to six years of age. Despite the large size, these boys are usually not strong or well coordinated and tend to have poor development of the pectoral and shoulder girdle musculature. Behavioral problems, especially temper tantrums and aggressive or defiant activity, start in early childhood and are sometimes augmented by dull mentality. Psychosexual problems are also more common. Severe acne is liable to develop at adolescence.

Though an XYY individual may manifest no evident abnormality, the likelihood of serious behavioral problems is significant. For example, among institutionalized male juvenile delinquents the incidence of XYY was 1:35, which is 24 times the frequency of XYY in newborn males.

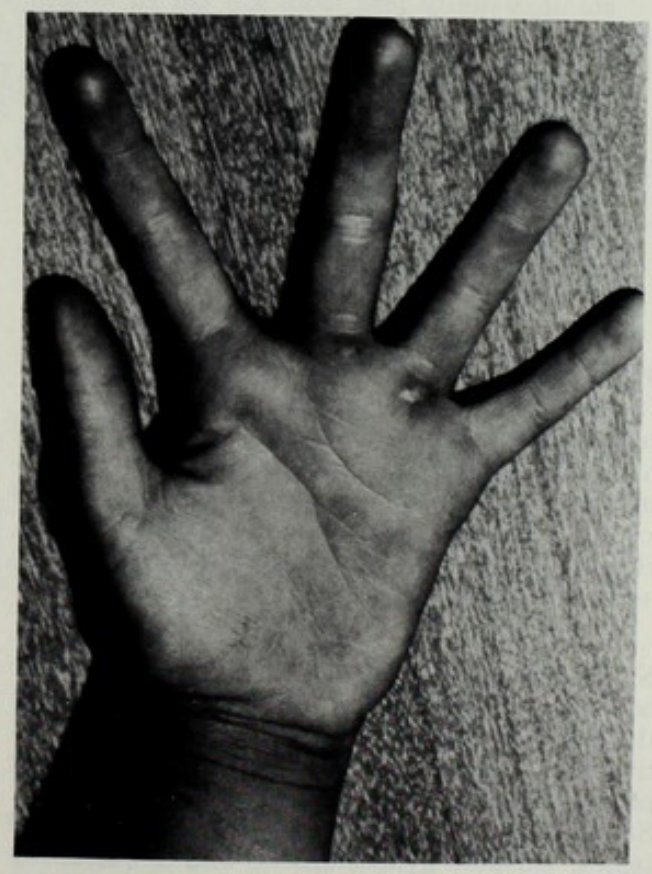
ETIOLOGY. XYY.

REFERENCES

1. Sandberg, A. A., Koepf, G. F., Ishihara, T., and Hauschka, T. S.: XYY human male. Lancet, *2*:488, 1961.
2. Osborne, R.: Personal communication.
3. Daly, R. F.: Neurological abnormalities in XYY males. Nature, *221*:472, 1969.
4. Valentine, G. H., McClelland, M. A., and Sergovich, F. R.: The growth and development of four XYY infants. Pediatrics, *48*:583, 1971.
5. Nielsen, J., Friedrich, U., and Zeuthen, E.: Stature and weight in boys with the XYY syndrome. Humangenetik, *14*:66, 1971.
6. Harrison, M. J. G., and Tennent, T. G.: Neurological anomalies in XYY males. Br. J. Psychiatry, *120*:447, 1972.
7. Voorhees, J. J., Wilkins, J. W., Jr., Hayes, E., and Harrell, F. R.: Nodulocystic acne as a phenotypic feature of the XYY genotype. Report of five cases, review of all known XYY subjects with severe acne, and discussion of XYY cytodiagnosis. Arch. Dermatol., *105*:913, 1972.







Eight year old boy, evaluated because of behavioral problems and poor school performance. Note the prominent glabella, relatively long face, and long fingers.

XXY SYNDROME, KLINEFELTER SYNDROME

Hypogenitalism and Hypogonadism, +/− Long Legs, Dull Mentality, and/or Behavioral Problems

This disorder, initially described by Klinefelter, et al.[1] in 1942, is now appreciated as being the most common single cause of hypogonadism and infertility, affecting about one in 500 males.

ABNORMALITIES

Performance. Tendency toward dull mentality with about 15 to 20 per cent of patients having an I.Q. below 80. Tendency toward behavior problems, especially immaturity, insecurity, shyness, poor judgment, and unrealistic boastful and assertive activity.

Growth. Tendency toward long limbs with low upper to lower segment ratio from childhood and relatively tall and slim stature. Without testosterone replacement therapy they tend to become obese as adults.

Hypogonadism with Hypogenitalism. Childhood: Relatively small penis and testes. Adolescence and Adulthood: Testes remain small, usually less than 2.5 cm in length. With rare exception, testosterone production is inadequate, with the average serum testosterone values in the adult being less than half the normal value. Infertility is the rule, with hyalinization and fibrosis of seminiferous tubules under excess gonadotrophin. Virilization is partial and inadequate with gynecomastia occurring in 40 per cent.

OCCASIONAL ABNORMALITIES. Genital: Cryptorchidism, hypospadias. Behavioral: Homosexuality. Other: Scoliosis during adolescent years. As adults, diabetes mellitus (8 per cent) and chronic bronchitis are more common. Mild to moderate ataxia occasionally occurs, as does ulcerative breakdown of the skin over the anterior lower legs.

NATURAL HISTORY. Dull mentality and/or behavioral problems are often not evident until the boy enters school. These features and relatively long limbs, small penis and/or small testes provide the clues toward diagnosis in childhood. Subsequently, inadequate virilization, small testes, variable gynecomastia, and a worsening of behavioral problems should provide even more obvious diagnostic clues.

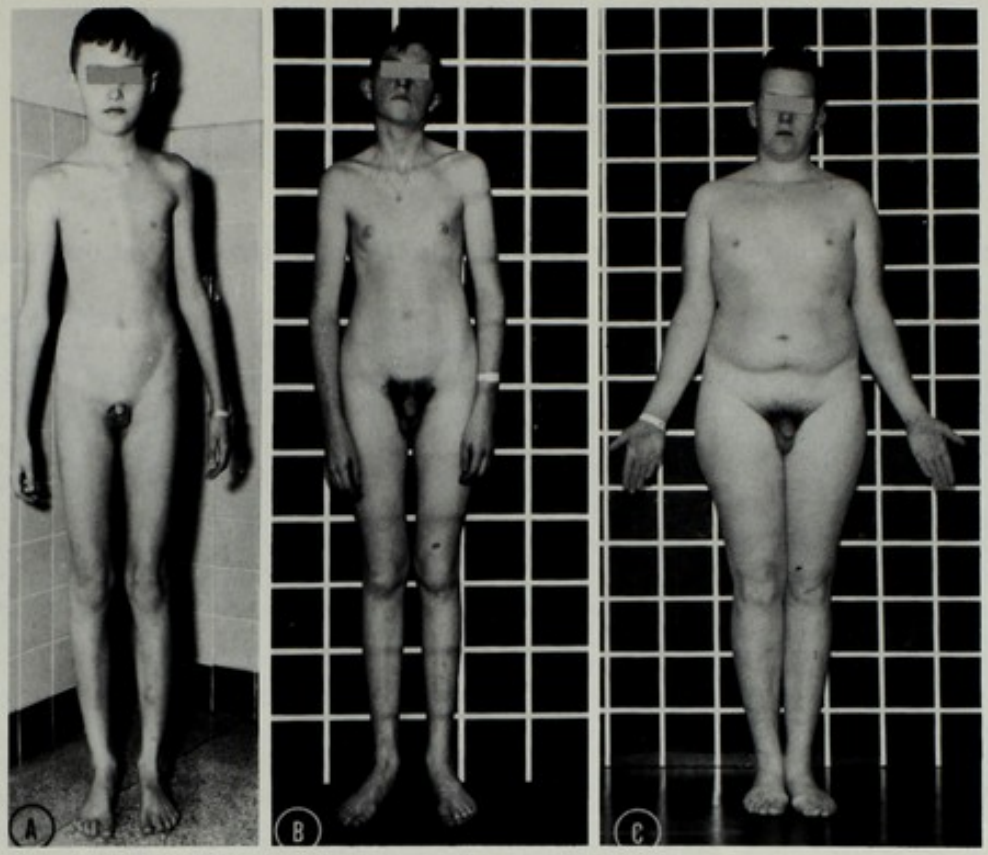
ETIOLOGY AND DIAGNOSIS. A buccal smear for X-chromatin is a satisfactory screening study. Any X-chromatin-positive male should have a chromosome study, ideally evaluating about 20 cells. Most will be XXY, but of X-chromatin-positive newborn males 22 per cent have been mosaics for XXY/XY. Such mosaic individuals have a better potential prognosis for testicular function. Other variants include XXYY, more likely to be mentally deficient and have behavioral problems, and XXXY, more likely to have mental deficiency, possible growth deficiency, and multiple minor anomalies including radioulnar synostosis at the elbow.

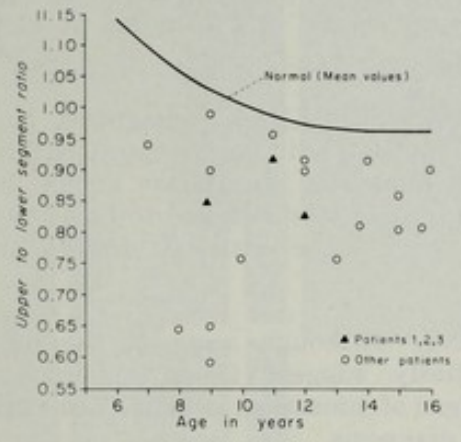
MANAGEMENT. Diagnosis during childhood of XXY (or XXYY or XXXY) syndrome is extremely helpful in allowing for prospective testosterone replacement therapy beginning at the age of 11 to 12 years. This will bring about a more usual adolescent development and prevent many of the features of adult Klinefelter syndrome which are due to testosterone insufficiency. The author's present practice is to give Depo-Testosterone every three weeks, starting with 25- and then 50-mg injections at about 11 years of age and increasing the dosage by 50-mg increments each year until an adult dosage of 250 mg is achieved at about 15 to 17 years of age.

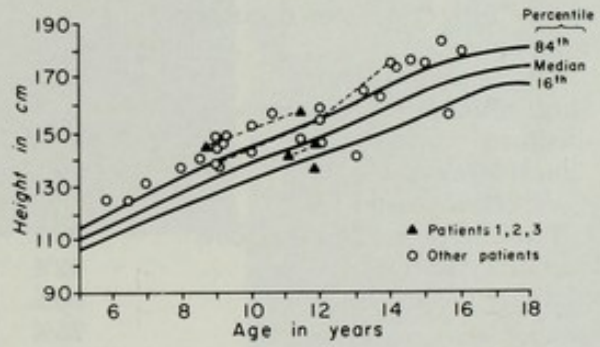
If the patient has XXY/XY mosaicism he should be evaluated during adolescence and testosterone replacement therapy only given if indicated by evidence of hypogonadism with inadequate virilization.

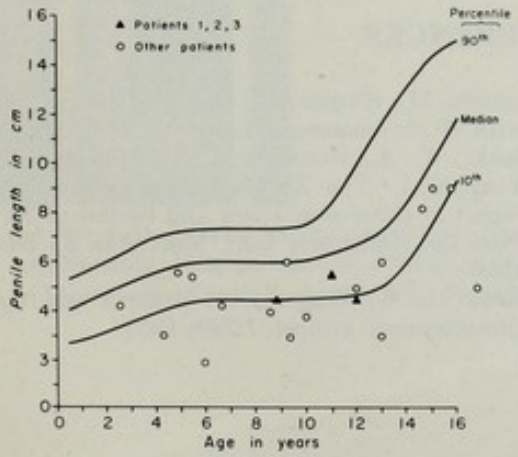
REFERENCES

1. Klinefelter, H. F., Jr., Reifenstein, E. C., Jr., and Albright, F.: Syndrome characterized by gynecomastia, aspermatatogenesis without aleydigism, and increased secretion of follicle-stimulating hormone (gynecomastia). J. Clin. Endocrinol. Metab., *2*:615, 1942.
2. Williams, R. H., ed.: Textbook of Endocrinology, 4th ed. Philadelphia, W. B. Saunders Co., 1968.
3. Caldwell, P. D., and Smith, D. W.: The XXY syndrome in childhood: Detection and treatment. J. Pediatr., *80*:250, 1972.
4. Borgaonkar, D. S., Mules, E., and Char, F.: Do the XXYY males have a characteristic phenotype? A review. Clin. Genet., *1*:272, 1970.

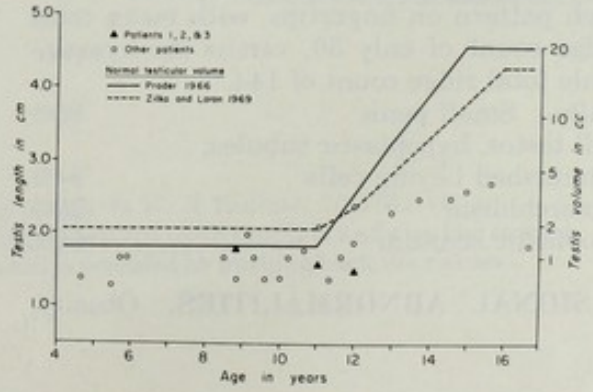








D



A, 9 year XXY child; note the small penis, long legs.
B, 16 year untreated XXY adolescent; note the gynecomastia and scoliosis.
C, 21 year untreated XXY adult; note the obesity, hypovirilization.
D, Measurements in XXY syndrome during childhood versus normals. (From Caldwell, P. D., and Smith, D. W.: J. Pediatr., *80*:250, 1972.)

XXXXY SYNDROME

Hypogenitalism, Limited Elbow Pronation, Low Dermal Ridge Count on Fingertips

Since the initial report of Fraccaro, et al.[1] in 1960, at least 40 cases of the XXXXY aneuploidy syndrome have been reported.

ABNORMALITIES.
Frequencies based on from 17 to 32 cases for each anomaly:[2]

Performance. Mental deficiency, intelligence quotient of 19 to 57, mean I.Q. of 34.
Hypotonia, joint laxity, or both, in about one third.

Growth. Tendency to low birth weight, shortness of stature, retarded osseous maturation	53%
Craniofacial. Sclerotic cranial sutures	57%
Wide-set eyes	80%
Upward slant, palpebral fissures	79%
Inner epicanthic folds	82%
Strabismus	59%
Low nasal bridge; wide or upturned nasal tip	95%
Mandibular prognathism	50%
Auricular anomaly (large, low-set, malformed)	70%
Neck. Short neck	72%
Thorax. Thick sternum	75%
Limbs. Limited pronation at elbow	95%
Radioulnar synostosis	42%
Clinodactyly of fifth finger	90%
Coxa valga	25%
Genu valga	50%
Pes planus	73%

Dermal ridge patterns.[3] High frequency of low arch pattern on fingertips, with mean total ridge count of only 50, versus the average male total ridge count of 144.

Genitalia. Small penis	80%
Small testes, hypoplastic tubules, diminished Leydig cells	94%
Cryptorchidism	28%
Hypoplastic scrotum	80%

OCCASIONAL ABNORMALITIES. Obesity, flat occiput, microcephaly, antimongoloid slant to palpebral fissures, Brushfield speckled iris, myopia, cleft palate, small peg-shaped teeth, web neck (12 per cent), pectus excavatum, congenital heart defect (especially patent ductus arteriosus), umbilical hernia, scoliosis, simian creases, club foot, abnormal toes, wide gap between first and second toes, hypospadias, bifid scrotum.

NATURAL HISTORY. Perinatal problems in adaptation have been frequent; linear growth is generally slow with moderately short final height attainment. Infertility and inadequate virilization may be anticipated. Depending on the overall life situation, testosterone replacement therapy should be considered at 11 to 12 years of age.

ETIOLOGY. The XXXXY diagnosis may be confirmed by the finding of as many as three X-chromatin masses in interphase nuclei (buccal smear) in a male who is found to have 49 chromosomes with three extra X group chromosomes.

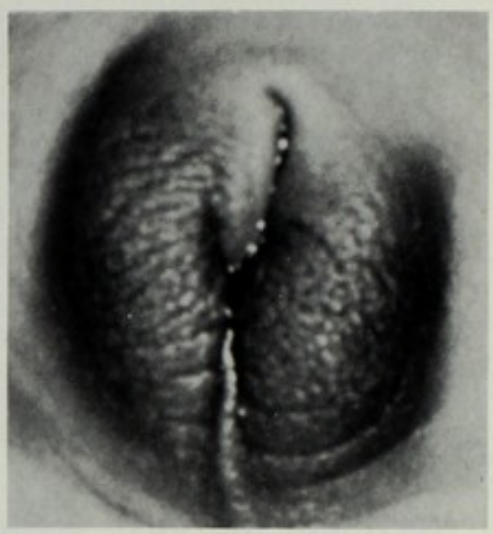
COMMENT. Although some of the features may initially suggest Down syndrome, the total pattern of anomalies is usually at variance with this diagnosis.

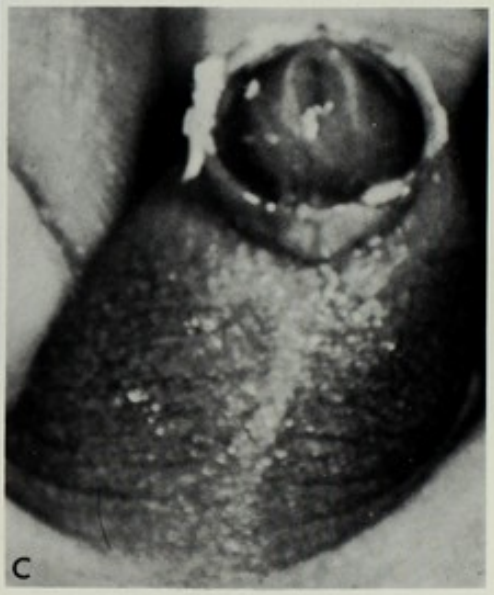
REFERENCES

1. Fraccaro, M., Kaijser, K., and Lindsten, J.: A child with 49 chromosomes. Lancet, *2*:899, 1960.
2. Zaleski, W. A., Houston, C. S., Pozsonyi, J., and Ying, K. L.: The XXXXY chromosome anomaly: report of three new cases and review of 30 cases from the literature. Can. Med. Ass. J., *94*:1143, 1966.
3. Penrose, L. S.: Finger-print pattern and the sex chromosomes. Lancet, *1*:298, 1967.









A, Six year old with height age of five years. (From Smith, D. W.: J. Pediatr., *70*:476, 1967.)
B, Neonate. Note club feet and small genitalia. He had delayed tooth eruption and also had eczema.
C, Genitalia of patient shown in *B*. The small penis was revealed by pushing back the tissues.

XXXX SYNDROME

Initially detected by Carr, et al. in 1961,[1] more than 20 cases have been reported.[2, 3] The phenotype has been quite variable, with the facies being suggestive of Down syndrome in several cases.

ABNORMALITIES. Other than mental deficiency all the other features have been variable. The patients are usually of normal stature.

Performance. I.Q. 30 to 80, average 55.

Facies. Midfacial hypoplasia, mild hypertelorism, epicanthal folds, mild micrognathia.

Limbs. Occasional fifth finger clinodactyly, radioulnar synostosis.

Other. Narrow shoulder girdle, occasional web neck. Variable amenorrhea, irregular menses.

NATURAL HISTORY. Besides mental deficiency, speech and behavioral problems are frequent.

ETIOLOGY. XXXX. A buccal smear for X-chromatin is an adequate screening test, realizing that only 6 to 9 per cent of the cells will show three X-chromatin masses.

REFERENCES

1. Carr, D. H., Barr, M. L., and Plunkett, E. R.: An XXXX sex chromosome complex in two mentally defective females. Can. Med. Assoc. J., *84*:131, 1961.
2. Telfer, M. A., Richardson, C. E., Helmken, J., and Smith, G. F.: Divergent phenotypes among 48, XXXX and 47,XXX females. Am. J. Hum. Genet., *22*:326, 1970.
3. Gardner, R. J. M., Veale, A. M. O., and Sands, V. E.: XXXX syndrome: Case report, and a note on genetic counselling and fertility. Humangenetik, *17*:323, 1973.



Six and one half year old XXXX girl.

XXXXX SYNDROME

(Penta X Syndrome)

Upward Slant to Palpebral Fissures, Patent Ductus Arteriosus, Small Hands with Clinodactyly of Fifth Fingers

The first description of an individual with XXXXX was by Kesaree and Wooley[1] in 1963. Six cases have been reported.

ABNORMALITIES.

Mental deficiency, moderate to severe.
Growth deficiency, especially postnatally.
Mild upward slant (mongoloid) to palpebral fissures. Low nasal bridge, short neck.
Small hands with mild clinodactyly of fifth fingers.
Patent ductus arteriosus.

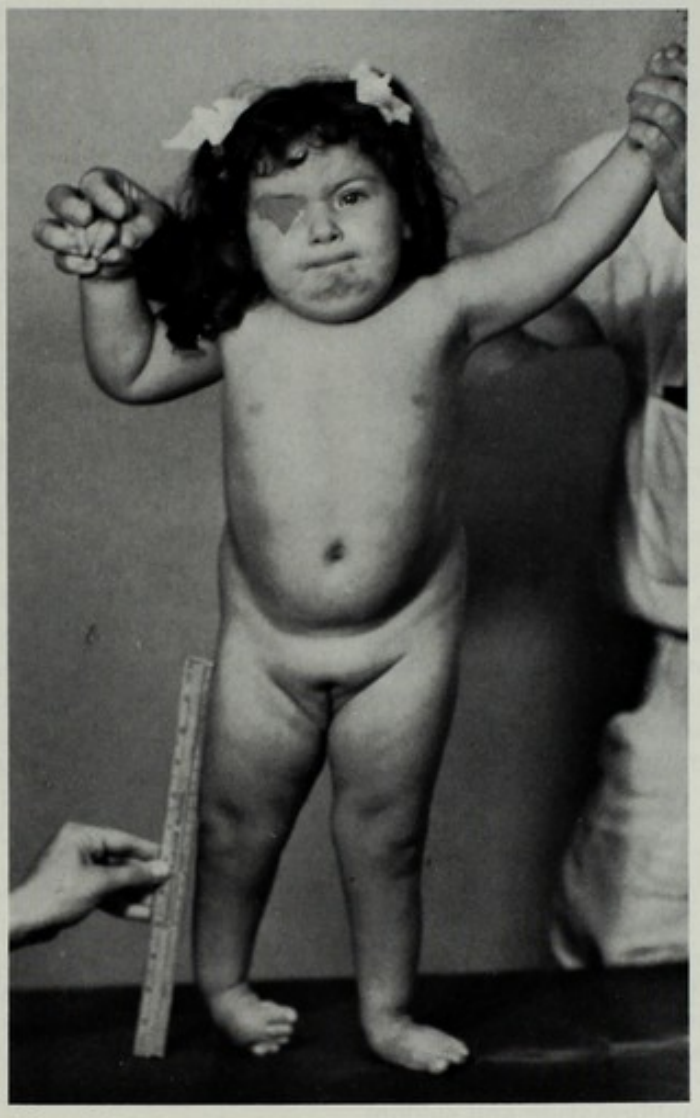
OCCASIONAL ABNORMALITIES. Colobomata of iris, hypertelorism, inner canthal folds, low-set ears, high frequency low arch dermal ridge patterns, simian creases, dislocation of elbow, equinovarus, overlapping toes.

NATURAL HISTORY. Variable, from failure to thrive to development such as noted in the figure.

COMMENT AND ETIOLOGY. Of interest is the occurrence in these XXXXX individuals of many of the nonspecific anomalies found in Down syndrome, a diagnosis which was initially considered in some of the patients. The finding of as many as four sex chromatin bodies in interphase nuclei in conjunction with three extra C group chromosomes in metaphase preparations establishes the presence of five X chromosomes.

REFERENCES

1. Kesaree, N., and Wooley, P. V.: A phenotypic female with 49 chromosomes, presumably XXXXX. A case report. J. Pediatr., *63*:1099, 1963.
2. Sergovich, F., Vilenberg, C., and Pozaonyi, J.: The 49,XXXXX chromosome constitution: Similarities to the 49,XXXXY condition. J. Pediatr., *78*:285, 1971.



Two and one third year old with height age of 18 months and a performance level of about one year. A patent ductus arteriosus had been repaired. The hands were small with incurved fifth fingers, and the ears were slightly low in placement. (From Brody, J., et al.: J. Pediatr., *70*:105, 1967.)

TURNER SYNDROME, XO SYNDROME

Short Female, Broad Chest with Wide Spacing of Nipples, Congenital Lymphedema or Its Residua

An association between small stature and defective ovarian development had been noted as early as 1922 by Rossle,[1] who classified the disorder under "sexagen dwarfism." A more expanded syndrome of small stature, sexual infantilism, webbed neck, and cubitus valgus in seven females was described by Turner[2] in 1938. The discovery of the chromosomal basis for the syndrome led to a more concise and expanded appreciation of the clinical phenotype of the XO syndrome, generally called the Turner syndrome.

Chromosomal studies of spontaneous abortuses have clearly shown that the majority of XO individuals die in the first few prenatal months. The precise reason for this early mortality has not been elucidated. At birth the incidence of sex chromatin negative females, presumably XO individuals, is 0.4 of 1000 females, or about 1 : 5000 newborns. Obviously this does not include many of the XO/XX mosaics or individuals with only a partial deletion of one X, who might be sex chromatin positive.

ABNORMALITIES. The following list of abnormalities, with the approximate percentage for each anomaly, includes those of the full monosomic XO syndrome. Patients with only a part of the cells XO (XX/XO mosaics, XY/XO mosaics with varying degrees of male type genitalia), or in whom only a part of one X is missing (X-isochromosome X or X-deleted X), generally have a lesser degree of malformation and seldom have such features as congenital lymphedema, webbed neck, or coarctation of the aorta. The most consistent features for the entire group are small stature and gonadal dysgenesis. Because the latter feature is not evident during childhood, a chromosomal study is indicated in any girl with short stature of unknown cause whose clinical phenotype is not incompatible with the XO syndrome.

Growth. Small stature, often evident by birth. (100 per cent).

Gonad. Ovarian dysgenesis with hypoplasia to absence of germinal elements (90+ per cent).

Lymph Vessels. Transient congenital lymphedema with residual puffiness over the dorsum of the fingers and toes (80+ per cent).

Thorax. Broad chest with widely spaced nipples which may be hypoplastic, inverted, or both (80+ percent); often mild pectus excavatum.

Auricles. Anomalous auricles, most commonly prominent (80+ per cent).

Facies. Narrow maxilla (palate) (80+ per cent).
Relatively small mandible (70+ per cent).
Inner canthal folds (40+ per cent).

Neck. Low posterior hairline, appearance of short neck (80+ per cent).
Webbed posterior neck (50 per cent).

Extremities. Cubitus valgus or other anomaly of elbow (70+ per cent).
Knee anomalies such as medial tibial exostosis (60+ per cent).
Short fourth metacarpal, metatarsal, or both (50+ per cent).

Other Skeletal. Bone dysplasia with coarse trabecular pattern, most evident at metaphyseal ends of long bones (50 + per cent).

Nails. Narrow, hyperconvex and/or deep set nails (70+ per cent).

Skin. Excessive pigmented nevi (50+ per cent).
Distal palmar axial triradii (40+ per cent).
Loose skin, especially about the neck in infancy (? per cent).

Renal. Most commonly horseshoe kidney, double or cleft renal pelvis, and minor alterations (60+ per cent).

Cardiac. Cardiac defect (20+ per cent), of which 70 per cent are coarctation of aorta.

CNS. Perceptive hearing impairment (50+ per cent).

OCCASIONAL ABNORMALITIES

Skeletal. Abnormal angulation of radius to carpal bones, Madelung's deformity, short midphalanx of fifth finger, short third to fifth metacarpals and/or metatarsals, scoliosis, kyphosis, spina bifida, vertebral fusion, cervical rib, abnormal sella turcica.

Eyes. Ptosis (16 per cent), strabismus, blue sclerae, cataract.

CNS. Mental retardation, about 10 per cent. Mean intelligence quotient about 95.

Other. Hemangiomata, rarely of the intestine. Idiopathic hypertension.

NATURAL HISTORY. The congenital lymphedema usually recedes in early infancy, leaving only puffiness over the dorsum of the fingers and toes, although rarely there may be recrudes-

cence of the lymphedema with estrogen replacement therapy. At birth the skin tends to be loose, especially in the posterior neck where excess skin may persist as the pterygium colli. Small size is often evident at birth, the mean birth weight being 2900 g. Linear growth proceeds at about half to three fourths the usual rate, there is usually no adolescent growth spurt, and final height of 50 to 60 inches with a mean of 55 inches is achieved at a usual age despite the roentgen evidence of "retarded osseous maturation." The relative stature of XO individuals is still influenced by the genetic background, the tallest sets of parents having the tallest XO children.

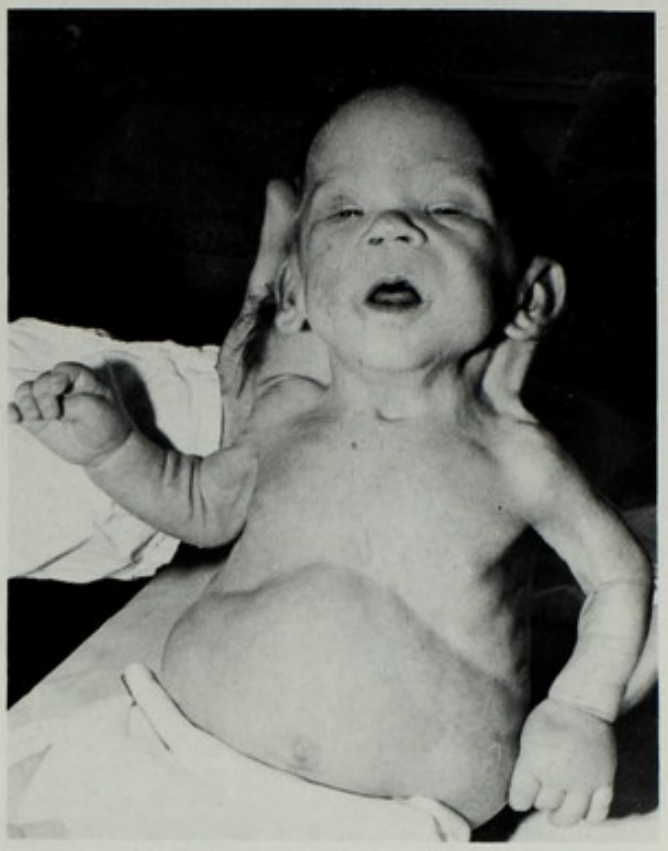
Studies of XO abortuses have disclosed near-normal development of the ovaries in early fetal life. Apparently they usually do not make primary follicles and the ovary degenerates rather rapidly.[4] By adolescence there is seldom any functional ovarian tissue remaining.

An occasional patient may show evidence of estrogen production at adolescence, although this is generally transient; at least one XO individual was fertile. Generally cyclic estrogen replacement therapy is indicated, beginning at the appropriate psychological time for each individual. Some investigators have recommended a period of low dosage androgen therapy prior to estrogen replacement,[5] in an effort to improve the rate of growth and final height attainment. Such therapy, if utilized, should be cautiously monitored in order to prevent undesirable virilization. At some time between eight years and adolescence these patients should be told that the ovaries are incompletely developed and that they should plan on adopting children and taking "the same kind of medicine the ovary makes" at adolescence.

The actual incidence of early mortality due to congenital heart defect is unknown because there is no large series of cases diagnosed from birth. The types of renal anomalies that occur generally pose no problem to health, which is generally good. Enhancement of physical appearance by plastic surgery for prominent inner canthal folds, protruding auricles, and especially for webbed neck should be given serious consideration prior to school age. The major psychological problem is usually the adaptation to shortness of stature, for which there is no effective treatment at present.

At the present time we do not have adequate information on longevity and cause of death beyond the age of childhood for individuals with the XO syndrome.

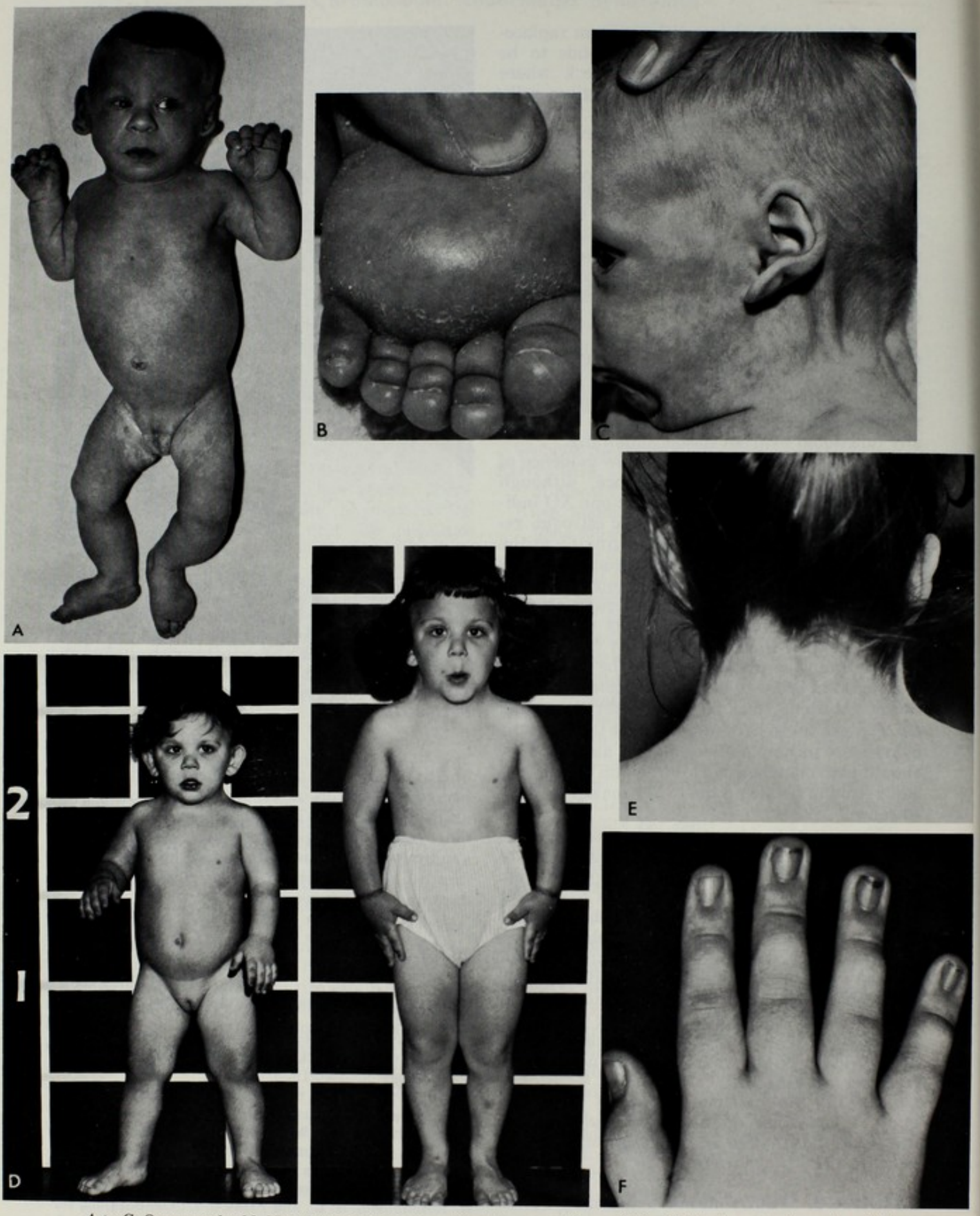
ETIOLOGY. Faulty chromosomal distribution leading to XO individual with 45 chromosomes. The paternal sex chromosome is more likely the one to be missing, as indicated by studies for X-linked gene expressions in the XO individuals and their parents. There has been no significant older maternal age factor for this aneuploidy syndrome. It is generally a sporadic event in a family, although there are as yet no adequate data on risk for recurrence.



Ten day old X0 patient who still has lymph-filled bilateral cysts in the posterior neck area, the cause for the web neck and for the prominent ears. This patient had abdominal muscle hypoplasia with bulging flanks, possibly secondary to earlier undue distention of the abdomen by fluid. Thus, this baby survived fetal life and was born with a more severe degree of lymphedema than usual.

REFERENCES

1. Rossle, R. I.: Wachstum und Altern. München, 1922.
2. Turner, H. H.: A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology, *23*:566, 1938.
3. Lindsten, J.: The nature and origin of X chromosome aberrations in Turner's syndrome. Stockholm, Almquist and Wiksell, 1963.
4. Weiss, L.: Additional evidence of gradual loss of germ cells in the pathogenesis of streak ovaries in Turner's syndrome. J. Med. Genet., *8*:540, 1971.
5. Rosenbloom, A. L., and Frias, J. L.: Oxandrolone for growth promotion in Turner syndrome. Am. J. Dis. Child., *125*:385, 1973.



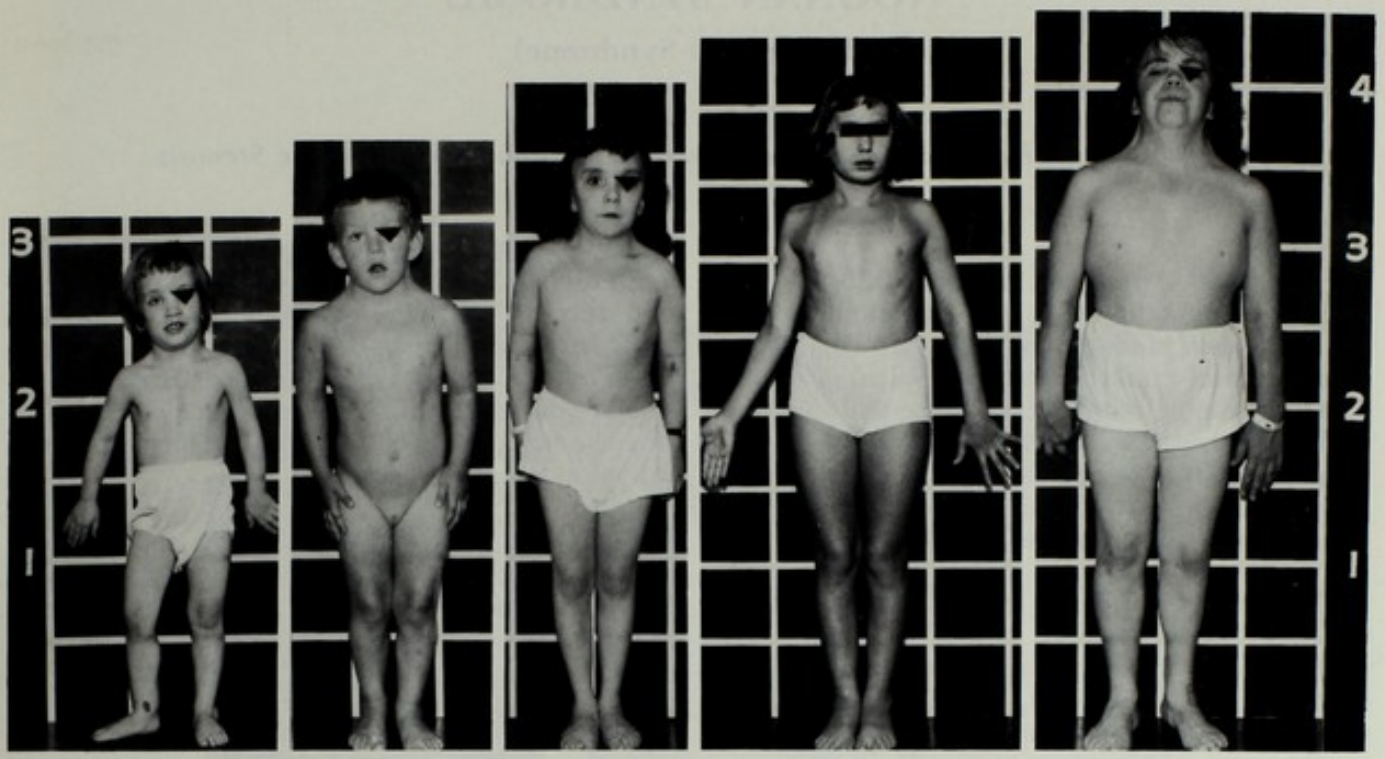
A to *C*, One month old. Note lymphedema, prominent ears, and loose folds of skin in posterior neck with low hair line.

D, Same girl at two years and at four years, with height ages of 17 months and three years respectively.

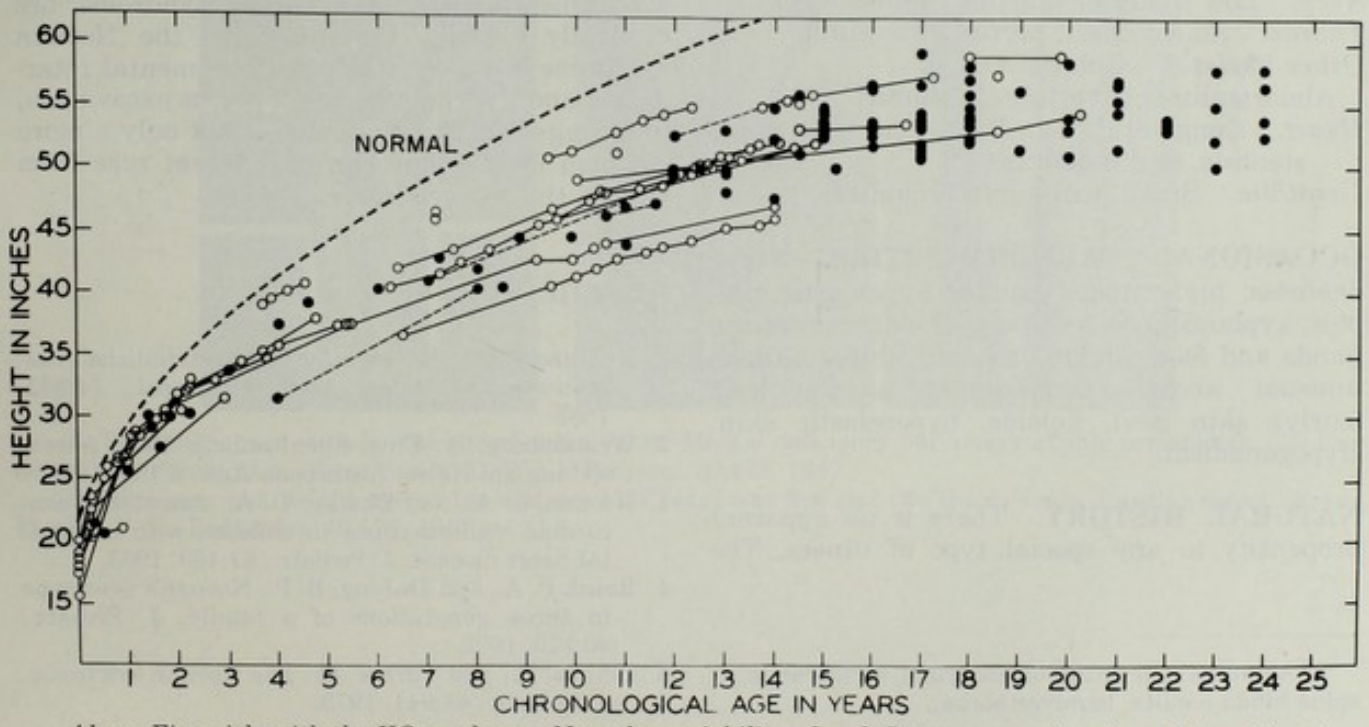
E, Low posterior hair line and residual lateral neck web.

F, Narrow, hyperconvex, deep-set fingernails; residual puffiness.

(*A* to *C*, *E*, and *F* from Lemli, L., and Smith, D. W.: J. Pediatr., *63*:577, 1963.)



3 years | 4 yr. 6 mos. | 10 yr. 5 mos. | 12 years | 14 yr. 10 mos.



Above, Five girls with the XO syndrome. Note the variability of such features as web neck and broad chest.

Below, Linear growth of girls with the XO syndrome. The open dots represent patients evaluated at the University of Wisconsin; the others were taken from the literature. (From Lemli, L., and Smith, D. W.: J. Pediatr., *63*: 577, 1963.)

NOONAN SYNDROME

(Turner-like Syndrome)

Webbing of the Neck, Pectus Excavatum, Cryptorchidism, Pulmonic Stenosis

Kobilinsky[1] reported in 1883 a 20 year old male with webbing of the neck, incomplete folding of the ears, and low posterior hairline, but no mention was made of other physical findings. The first complete description appears to be that of Weissenberg[2] in 1928. In recent years the disorder often has been termed the Noonan syndrome in order to more clearly distinguish this clinical condition from the XO Turner syndrome.

ABNORMALITIES

Growth. Short stature

Performance. Mental retardation.

Facies. Epicanthic folds, ptosis of eyelids, hypertelorism, myopia, keratoconus, strabismus.

Low-set and/or abnormal auricles. Anterior dental malocclusion.

Neck. Low posterior hairline, webbed neck.

Thorax. Shield chest, pectus excavatum.

Other Skeletal. Cubitus valgus.

Abnormalities of vertebral column*

Heart. Congenital heart disease (pulmonic stenosis, septal defects).

Genitalia. Small penis, cryptorchidism.

OCCASIONAL ABNORMALITIES. Nerve deafness; high arched palate; hypoplastic nipples; kyphoscoliosis; edema of the dorsum of the hands and feet; simian creases; cubitus valgus; unusual wool-like consistency of the hair (curly); skin nevi, keloids, hyperelastic skin. Hypogonadism.

NATURAL HISTORY. There is no apparent propensity to any special type of illness. The degree of mental retardation is seldom severe, and the social performance is usually better than anticipated from the intelligence quotient.

The reported findings from testicular biopsies are difficult to interpret in terms of function because most have been performed in prepubertal or undescended testes.

ETIOLOGY. Unknown. Usually a sporadic occurrence within families. Apparent autosomal dominant inheritance has occasionally been documented. Perhaps closer scrutiny will reveal several clinical entities within the rather loose designation, the Noonan syndrome.

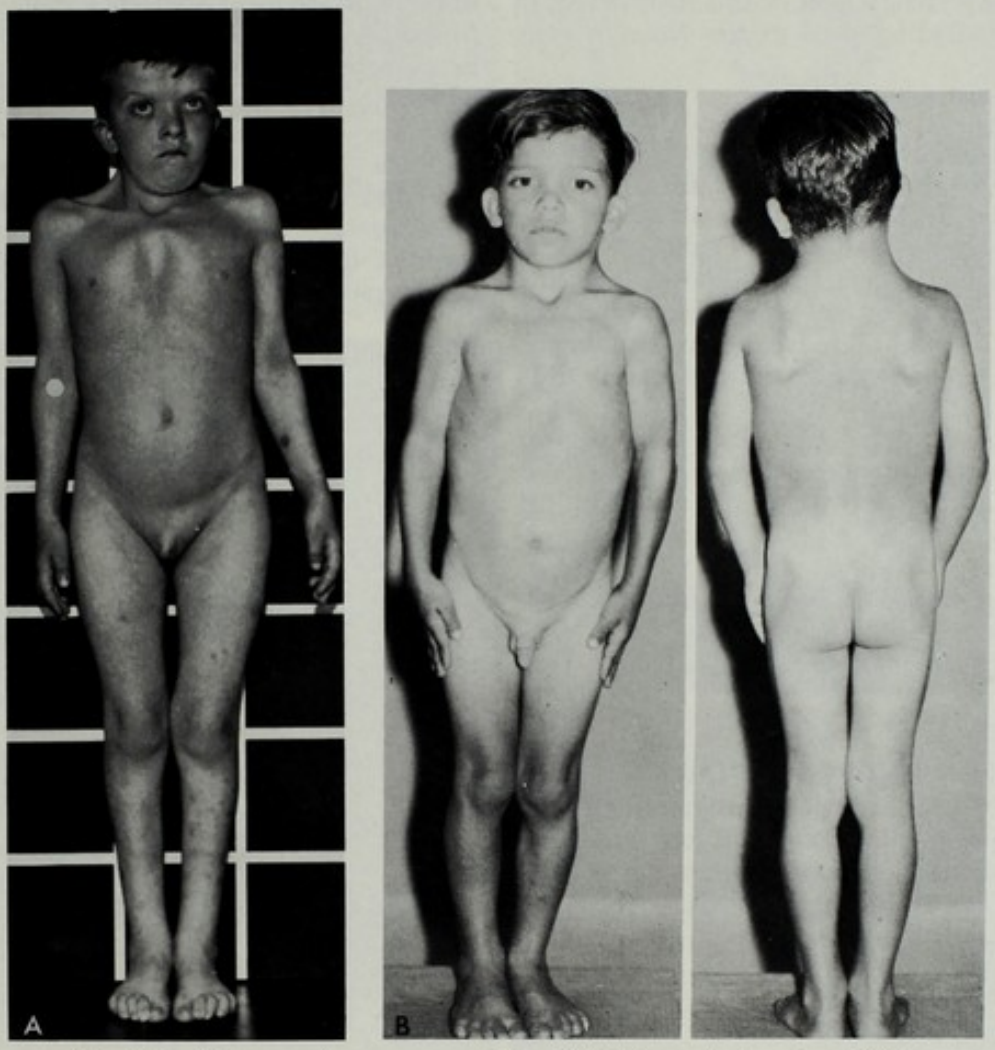
The most likely condition to be confused with this syndrome is the XO/XY mosaicism.

COMMENT. General differences between this syndrome and the XO Turner syndrome are clinically evident. Patients with the Noonan syndrome are more likely to have mental retardation and a serious degree of pectus excavatum, and congenital heart disease is not only a more common feature but also of different type from that in the XO syndrome.

*Abnormal curvature or abnormal vertebrae (e.g., spina bifida occulta, hemivertebrae).

REFERENCES

1. Kobilinsky, O.: Ueber eine flughautahnliche Ausbreitung am Halse. Arch. Anthropol., *14*:343, 1883.
2. Weissenberg, S.: Eine eigentumliche Haut faltenbildung am Halse. Anthropol. Anz., *5*:141, 1928.
3. Noonan, J. A., and Ehmke, D. A.: Associated noncardiac malformations in children with congenital heart disease. J. Pediatr., *63*:469, 1963.
4. Baird, P. A., and DeJong, B. P.: Noonan's syndrome in three generations of a family. J. Pediatr., *80*:110, 1972.
5. Collins, E., and Turner, G.: The Noonan syndrome. J. Pediatr., *83*:941, 1973.



A, Twelve year old with height age of seven years. Mental deficiency but a very affable personality. Cardiac defect. Cryptorchidism. (From Smith, D. W.: J. Pediatr., *70*:473, 1967.)

B, Nine year old; height age at ten and one half years was five and two thirds years. Cardiac defect. (From Ferrier, P. E.: Pediatrics, *40*:575, 1967.)

AARSKOG SYNDROME

Hypertelorism, Brachydactyly, Shawl Scrotum

Set forth by Aarskog in 1970,[1] there has been increasing recognition of this disorder.[2–4] It can easily be misdiagnosed as the Noonan syndrome.

ABNORMALITIES

Growth. Mild to moderate short stature.

Facies. Rounded. Hypertelorism with variable ptosis of eyelids, and slight downward slant to palpebral fissures. Small nose with anteverted nares, broad philtrum, maxillary hypoplasia, slight crease below the lower lip. Upper helices of ears incompletely outfolded.

Limbs. Brachydactyly with clinodactyly of fifth fingers, unusual position of extended fingers, simian crease, mild interdigital webbing.

Thorax. Mild pectus excavatum.

Abdomen. Prominent umbilicus, inguinal herniae.

Genitalia. "Shawl" scrotum (see figure), cryptorchidism.

OCCASIONAL ABNORMALITIES

Skeletal. Cervical vertebral anomalies, scoliosis, cubitus valgus, splayed toes with bulbous tips, and metatarsus adductus.

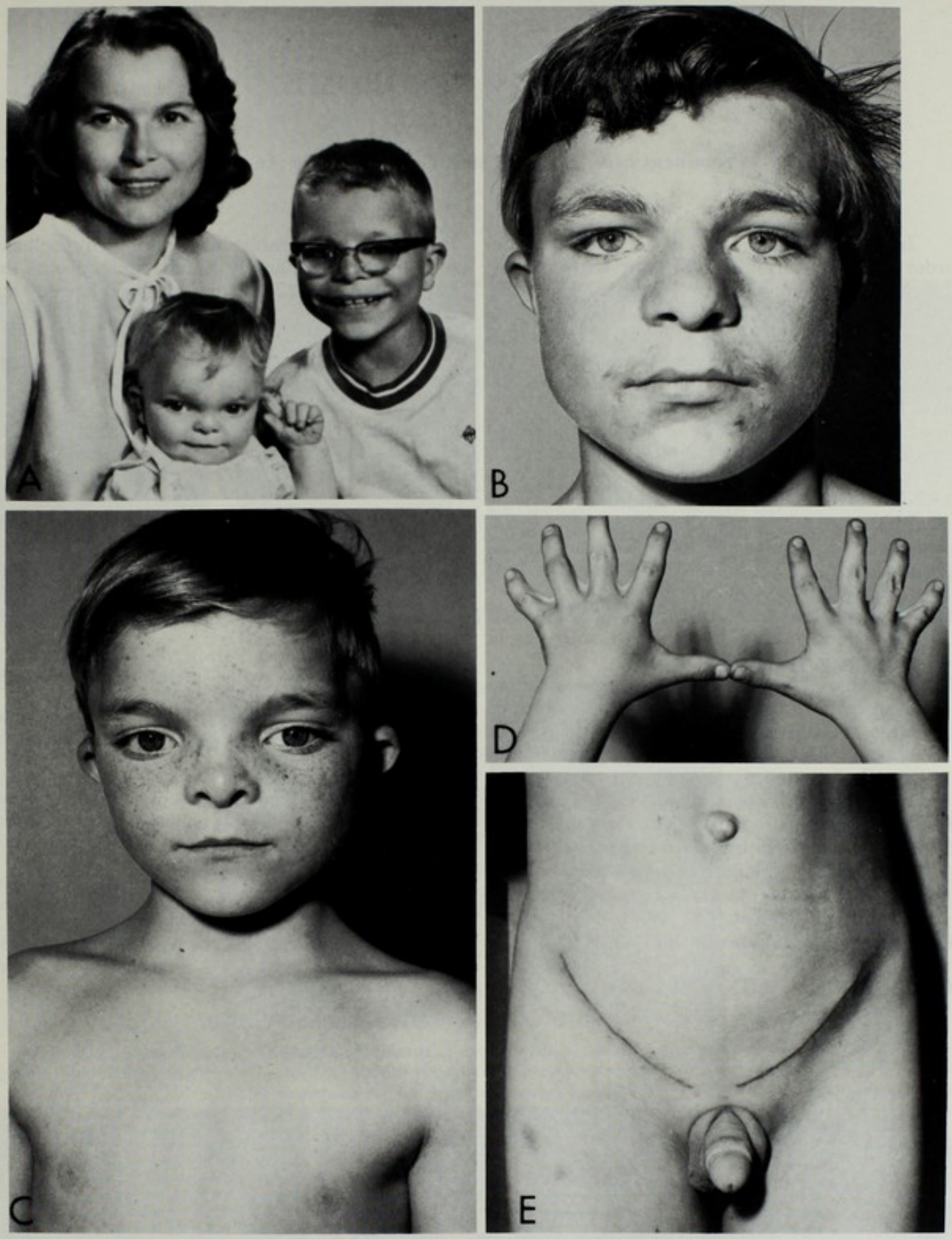
Genitalia. Cleft scrotum, phimosis.

NATURAL HISTORY. Growth deficiency may be of prenatal onset but more commonly is first evident at one to three years of age and may be associated with slow maturation and a late advent of adolescence. Though serious mental deficiency is unusual, mild degrees have been a variable feature. Social performance is usually good and they tend to have a pleasant personality. There is the suspicion of reduced fertility in some of the affected males, possibly related to the cryptorchidism.

ETIOLOGY. X-linked semidominant inheritance is implied, with carrier females often showing some minor manifestations of the disorder, especially in the facies or hands.

REFERENCES

1. Aarskog, D.: A familial syndrome of short stature associated with facial dysplasia and genital anomalies. J. Pediatr., *77*:856, 1970.
2. Scott, C. I., Jr.: Unusual facies, joint hypermobility, congenital anomaly, and short stature: A new dysmorphic syndrome. Birth Defects, *7*:240, 1971.
3. Furukawa, C. T., Hall, B. D., and Smith, D. W.: The Aarskog syndrome. J. Pediatr., *81*:1117, 1972.
4. Sugarman, G. I., Rimoin, D. L., and Lackman, R. S.: The facial-digital-genital (Aarskog) syndrome. Am. J. Dis. Child., *126*:248, 1973.



A, Mother with mild hypertelorism and widow's peak and two affected sons showing more striking hypertelorism.

B, Sixteen year old, shown as a boy in *A*. Note the mild flare of the medial eyebrow and the less pronounced appearance of hypertelorism with age.

C, Seven year old, shown as an infant in *A*. Note the mild overfolding of the ear helixes and the mild pectus excavatum.

D, Mild brachyclinodactyly with mild syndactyly in patient shown in *C*.

E, "Pouting" umbilicus, scars of inguinal hernia repairs, and "shawl" scrotum in an eight year old boy.

(From Furukawa, C. T., et al.: J. Pediatr., *81*:1117, 1972.)

WILLIAMS SYNDROME

Prominent Lips, Hoarse Voice, Cardiovascular Anomaly

In 1961, Williams, et al. described this disorder in four unrelated children with mental deficiency, an unusual facies, and supravalvular aortic stenosis. Subsequently, well over 100 cases have been described. Hypercalcemia has been an infrequent finding; cardiovascular anomalies, including supravalvular aortic stenosis, have been variable, and features such as aberrations of growth, performance, and the unusual facies are more consistent relative to diagnosis.

ABNORMALITIES. Varying features from the following:

Growth. Mild prenatal growth deficiency. Postnatal growth rate about 75 per cent of normal. Mild microcephaly.

Performance. Average I.Q. about 56. Friendly, loquacious personality, hoarse voice, mild neurologic dysfunction.

Facies. Medial eyebrow flare, short palpebral fissures. Depressed nasal bridge. Epicanthal folds. Periorbital fullness of subcutaneous tissues. Blue eyes, stellate pattern in the iris. Anteverted nares, long philtrum, prominent lips with open mouth.

Limbs. Hypoplastic nails, hallux valgus.

Cardiovascular. Supravalvular aortic stenosis, peripheral pulmonary artery stenosis, pulmonic valvular stenosis, ventricular and atrial septal defect.

Dentition. Partial anodontia.

OCCASIONAL. ABNORMALITIES. Ocular hypotelorism, strabismus, malar hypoplasia, fifth finger clinodactyly, small penis, pectus excavatum, inguinal and/or umbilical hernia, hypercalcemia.

NATURAL HISTORY. In early infancy these children tend to be fretful and have feeding problems. During childhood they tend to be outgoing and loquacious, a personality referred to as "cocktail party manner." About one sixth, however, have severe behavior problems.

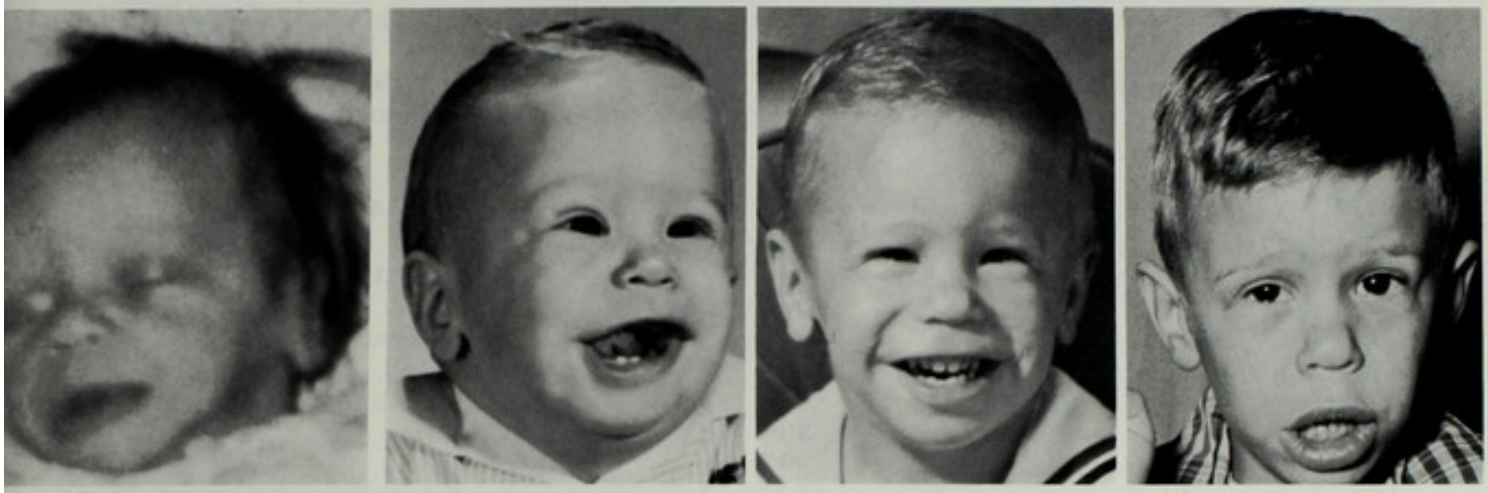
ETIOLOGY. Unknown. All cases have been sporadic.

REFERENCES

1. Joseph M. C., and Parrott, D.: Severe infantile hypercalcaemia with special reference to the facies. Arch. Dis. Child., *33*:385, 1958.
2. Williams, J. C. P., Barratt-Boyes, B. G., and Lowe, J. B.: Supravalvular aortic stenosis. Circulation, *24*:1311, 1961.
3. Beuren, A. J., Schulze, C., Eberle, P., Harmjanz, D., and Opitz, J.: The syndrome of supravalvular aortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance. Am. J. Cardiol., *13*:471, 1964.
4. Fraser, D., Langford Kidd, B. S., Kooh, S. W., and Paunier, L.: A new look at infantile hypercalcemia. Pediatr. Clin. North Am., *13*:503, 1966.
5. Jones, K. L., and Smith, D. W.: The Williams elfin facies syndrome. A new perspective. J. Pediatr., *86*:718, 1975.



Stellate pattern to iris, relatively short nails, and valgus position of big toe—frequent features in Williams syndrome.



2 weeks | 6 months | 2 years | 4 years
Height age – 2 5/6 yr.



A, Facial appearance from the mother's photos of a boy with aortic stenosis, unusual facies, and relatively slow developmental progress. The serum calcium is presently normal; unknown during infancy.

B, Four and one half month old with severe hypercalcemia whose height age was four months at seven months of age when the baby died. Necropsy showed nonspecific fibrous thickening in the intima of the aortic valve. (From Joseph, M. C., and Parrott, D.: Arch. Dis. Child., *33*:385, 1958.)

C, Seventeen year old mentally deficient boy of short stature who has evidence of supravalvular aortic stenosis. (Courtesy of A. Reichert, Rainier State Training School, Buckley, Washington.)

DE LANGE SYNDROME

(Cornelia de Lange Syndrome, Brachmann–de Lange Syndrome)

Synophrys, Thin Downturning Upper Lip, Micromelia

The syndrome was originally described in 1933 by Cornelia de Lange.[1] More than 150 cases have been reported.

ABNORMALITIES

Growth. Shortness of stature of prenatal onset	100%
Retarded osseous maturation	50%
Performance. Mental retardation and sluggish physical activity	100%
Initial hypertonicity	100%
Low pitched weak growling cry in infancy	100%
Cranium. Microbrachycephaly	93%
Eyes. Bushy eyebrows and synophrys	99%
Long, curly eyelashes	100%
Nose. Small nose, anteverted nostrils	100%
Mouth. Characteristic lips and mouth*	100%
High arched palate	50%
Mandible. Micrognathia	97%
Spurs in the anterior angle of the mandible, prominent symphysis	66%
Skin. Hirsutism	97%
Cutis marmorata and perioral pale "cyanosis"	64%
Hypoplastic nipples and umbilicus	7/7
Hands and Arms. Micromelia	69%
Phocomelia and oligodactyly	30%
Clinodactyly of fifth fingers	69%
Simian crease	84%
Proximal implantation of thumbs	81%
Flexion contracture of elbows	84%
Feet. Micromelia	99%
Syndactyly of second and third toes	81%
Male Genitalia. Hypoplasia	4/17
Undescended testes	15/26

OCCASIONAL ANOMALIES. Seizures (20 per cent), myopia, microcornea, astigmatism, optic atrophy, coloboma of the optic nerve, strabismus, proptosis, choanal atresia, low-set ears, cleft palate, congenital heart defect (17 per cent, most commonly VSD), hiatus hernia, duplication of gut, malrotation of colon, brachyesophagus, pyloric stenosis, inguinal hernia, small labia majora, radial hypoplasia, short first metacarpal, and absent second to third interdigital triradius.

NATURAL HISTORY AND MANAGEMENT. These patients show a marked retardation of growth, evident by the time of birth, and as a rule they fail to thrive. Their intellectual performance is usually severely limited. The gait tends to be broad-based. They sometimes show autistic behavior, including self-destructive tendencies. The I.Q. varies from 4 to 85, with the majority being below 35. Those with the higher I.Q.'s tend to be the ones with a better birth weight and head circumference.[4] Episodes of aspiration in infancy, and increased susceptibility to infections appear to constitute the major hazards for survival in these patients.

ETIOLOGY AND RECURRENCE RISK. Unknown. Usually sporadic, the empiric recurrence risk is in the range of 1 to 3 per cent. Clinically there appears to be a gradation in severity and it is very difficult to be secure about a diagnosis in the more mildly affected cases.

COMMENT. The different functional abnormalities that have been reported in some patients, e.g., endocrine, hematologic, immunologic, represent another indication of the widespread effect of this condition in the patient.

*Thin lips with small midline beak of the upper and corresponding notch in the lower lip; downward curving of the angle of the mouth.

REFERENCES

1. de Lange, C.: Sur un type nouveau de génération (typus Amstelodamensis). Arch. Med. Engant., *36*:713, 1933.
2. Ptacek, L. J., Opitz, J. M., Smith, D. W., Gerritsen, T., and Waisman, H. A.: The Cornelia de Lange syndrome. J. Pediatr., *63*:1000, 1963.
3. Vischer, D.: Typus degenerativus Amstelodamensis (Cornelia de Lange syndrome). Helv. Paediatr. Acta, *20*:415, 1965.
4. Barr, A. N., et al.: Neurologic and psychometric findings in Brachmann-de Lange syndrome. Neuropaediatrie, *3*:46, 1971.





A, Neonate with small hands and feet.
B, Three month old with newborn length.
C, Five and one half year old with height age of two years and severe defect of right distal limb.
D, Similar facies of four affected individuals.
(From Ptacek, L. J., et al.: J. Pediatr., *63*:1000, 1963.)

RUBINSTEIN-TAYBI SYNDROME

Broad Thumbs and Toes, Slanted Palpebral Fissures, Hypoplastic Maxilla

Rubinstein and Taybi set forth this clinical entity in 1963.[1] More than 114 cases have been reported.

ABNORMALITIES

Growth. Short stature	79%
Retarded osseous maturation	94%
Performance. I.Q. 17 to 86.	
EEG abnormality	60%
Cranium. Small	84%
Facies. Palpebral fissures slant downward	100%
Maxilla hypoplastic with narrow palate	100%
Beaked nose with nasal septum extending below alae	68%
Epicanthic folds	62%
Strabismus	79%
Refractive error	58%
Auricles low-set and/or malformed	84%
Hands and Feet. Broad thumbs with radial angulation and broad toes	100%
Other fingers and toes broad	50%
Excess dermal ridge patterning in thenar and first interdigital areas of palm	50%
Pelvis. Low acetabular angle, flare to ilia	?
Genitalia. Cryptorchidism	100%
Skin. Nevus flammeus	54%

OCCASIONAL ABNORMALITIES

Skeletal. Prominent forehead, large anterior fontanel, large foramen magnum, parietal foramina, micrognathia, sternal anomalies, unfused arch of first cervical vertebra and other vertebral anomalies, scoliosis, syndactyly, polydactyly, clinodactyly of fifth finger.

Other. Cataract, coloboma, ptosis of eyelid, long eyelashes and hypertrichosis, simian crease, distal axial triradius, cardiac anomaly, renal anomaly, angulated penis, kyphoscoliosis, seizures, absence of corpus callosum.

NATURAL HISTORY. Respiratory infections and feeding difficulties are frequent problems in infancy. The degree of mental deficiency is variable, the most usual intelligence quotient being in the 40 to 50 range.

ETIOLOGY. Unknown. From 112 families there is one presumed recurrence, a crude recurrence risk of about one per cent.

REFERENCES

1. Rubinstein, J. H., and Taybi, H.: Broad thumbs and toes and facial abnormalities. A possible mental retardation syndrome. Am. J. Dis. Child., *105*: 588, 1963.
2. Rubinstein, J. H.: The broad thumbs syndrome—Progress report 1968. Birth Defects, *5*:25, 1969.
3. Simpson, N. E., and Brissenden, J. E.: The Rubinstein-Taybi syndrome: Familial and dermatoglyphic data. Am. J. Hum. Genet., *25*:225, 1973.



A, Three and one half year old. Height age of two years. I.Q., 45. Slight downslant to palpebral fissures.
B, Hand and foot on patient shown in *A*.
C, Change in facies from birth to several years of age. Note broad thumb at birth.
D, Change in facies from three and one half to 14 years.
(*C* and *D* are gratefully acknowledged to J. Rubinstein, Cincinnati.)

RUSSELL-SILVER SYNDROME

(Silver Syndrome)

Short Stature of Prenatal Onset, Skeletal Asymmetry, Small Incurved Fifth Finger

This pattern of malformation was independently described by Russell[1] and by Silver, et al.[2] in 1953–54. Silver emphasized the skeletal asymmetry as a feature of the disorder. This was a variable finding in the patients described by Russell. Gareis, et al.[4] have summarized the data on this syndrome and also noted that asymmetry of the prenatal onset growth deficiency is a variable feature in this disorder.

ABNORMALITIES

Growth and Skeletal. Small stature, prenatal onset.

Immature osseous development in infancy and early childhood, with late closure of anterior fontanel.

Asymmetry, most commonly of limbs.

Short and/or incurved fifth finger.

Facies. Small triangular facies with downturning corners of mouth. The sclerae may be bluish in early infancy.

Skin. Café-au-lait spots.

Other. Tendency toward excess sweating, especially on the head and upper trunk, during infancy. Liability to fasting hypoglycemia from about ten months until two to three years of age.

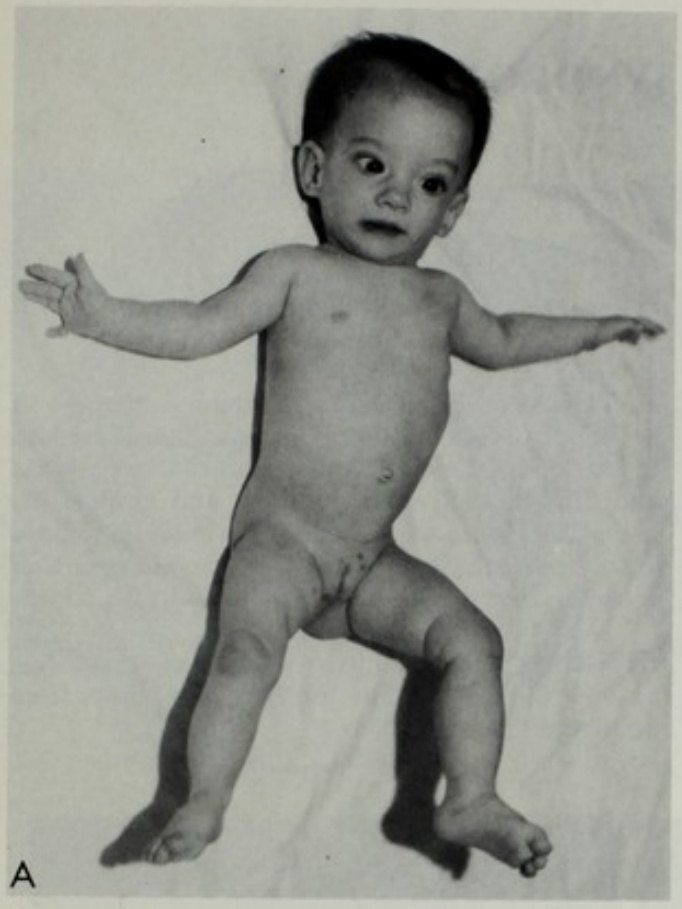
OCCASIONAL ABNORMALITIES. Syndactyly of second to third toes, renal anomaly, hypospadias.

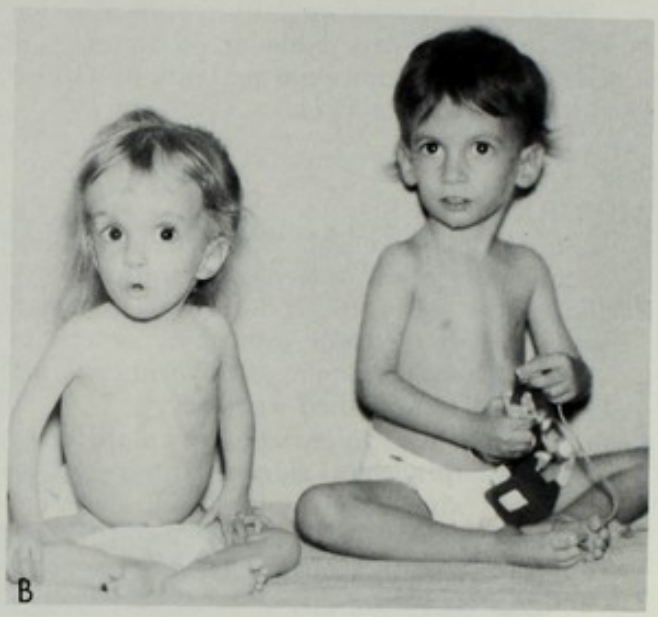
NATURAL HISTORY. The patients are usually slim and underweight for length during early childhood. There tends to be a gradual improvement in growth rate and appearance during childhood, and especially during adolescence. Final height attainment can be up to five feet. During infancy they tend to be weak and may be slow in major motor progress. Hence there is the risk of mental deficiency being implied, whereas intelligence is usually normal. Because of the small facies the upper head may *appear* large, though head circumference is well within the normal range. This appearance, plus the relatively large fontanels in early infancy, may give rise to a false impression of hydrocephalus—which they do not have. Somewhat frequent feedings and assurance of glucose intake during illnesses are often merited from six months of age until three years, the period of enhanced liability to fasting hypoglycemia for these patients.

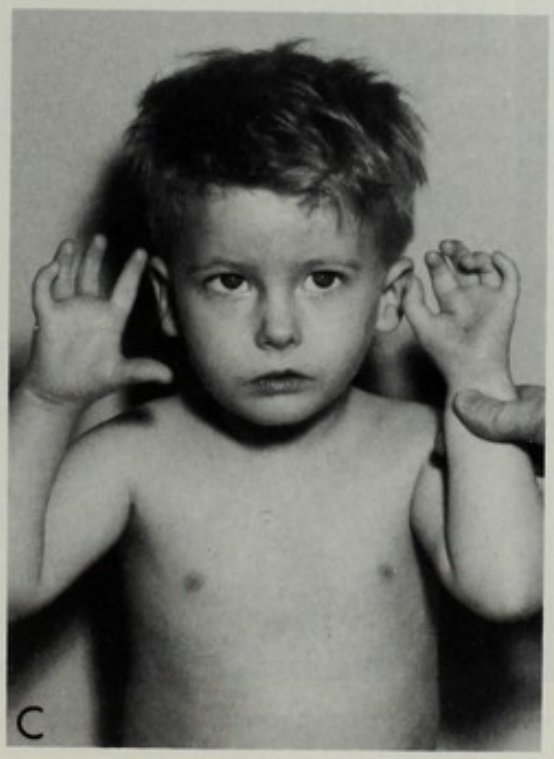
ETIOLOGY. Unknown, may be heterogeneous. It is usually a sporadic occurrence in an otherwise normal family. Autosomal dominant inheritance has been implied in at least one family.

REFERENCES

1. Russell, A.: A syndrome of "Intra-uterine" dwarfism recognizable at birth with craniofacial dysostosis, disproportionately short arms and other anomalies. Proc. R. Soc. Med., *47*:1040, 1954.
2. Silver, H. K., et al.: Syndrome of congenital hemihypertrophy, shortness of stature and elevated urinary gonadotrophins. Pediatrics, *12*:368, 1953.
3. Silver, H. K.: Asymmetry, short stature, and variations in sexual development. A syndrome of congenital malformations. Am. J. Dis. Child., *107*: 495, 1964.
4. Gareis, F. J., Smith, D. W., and Summitt, R. L.: The Russell-Silver syndrome without asymmetry. J. Pediatr., *79*:775, 1971.
5. Haslam, R. H. A., Berman, W., and Heller, R. M.: Renal abnormalities in the Russell-Silver syndrome. Pediatrics, *51*:216, 1973.









A, Six month old; height age, two months. Asymmetric leg length. (From Smith, D. W.: J. Pediatr., *70*:483, 1967.)

B, Seventeen month old girl with height age of six months and two year old boy with height age of fifteen months. Neither has asymmetry. Note the small facies, slimness and "loose" sitting posture. (From Gareis, F. J., et al.: J. Pediatr., *79*:775, 1971.)

C, Three and three fourths year old; height age, one and one half years. Note slight facial asymmetry.

D, Six year old with height age of two years. Note clinodactyly of fifth fingers. (Courtesy of J. Aase, University of Washington.)

DUBOWITZ SYNDROME

Peculiar Facies, Infantile Eczema, Small Stature, and Mild Microcephaly

This disorder was initially reported by Dubowitz[1] in 1965 with a follow-up on his case and a report of three additional patients by Grosse, Gorlin, and Opitz[2] in 1971.

ABNORMALITIES

Growth. Prenatal onset of growth deficiency, variable retarded osseous maturation.

Performance. Mild to moderate mental deficiency with tendency toward hyperactivity, short attention span, stubbornness, and shyness. High-pitched weak cry.

Craniofacial. Mild microcephaly, small facies, shallow supraorbital ridge with nasal bridge at about same level as forehead, short palpebral fissures with lateral telecanthus and appearance of hypertelorism, variable ptosis and blepharophimosis, and micrognathia.

Skin and Hair. Eczema-like skin disorder on face and flexural areas. Sparsity of hair, especially lateral eyebrows.

Dentition. Lag in eruption, carious.

Other Variable Features. Submucous cleft palate, pes planus, metatarsus adductus, hypospadias, cryptorchidism, clinodactyly of fifth finger, pilonidal dimple.

NATURAL HISTORY. Eczema, noted in three out of four patients, largely cleared by two to four years. Teeth became carious, two patients had diarrhea in early infancy, and rhinorrhea and otitis media were frequent problems. Behavioral aberrations with lag in development of speech posed the greatest problems in function.

ETIOLOGY. Presumed autosomal recessive, based on affected male and female siblings from unaffected parents.

REFERENCES

1. Dubowitz, V.: Familial low birth weight dwarfism with an unusual facies and a skin eruption. J. Med. Genet., *2*:12, 1965.
2. Grosse, R., Gorlin, J., and Opitz, J. M.: The Dubowitz syndrome. Z. Kinderheilkd., *110*:175, 1971.
3. Opitz, J. M., Pfeiffer, R. A., Hermann, J. P. R., and Kushnick, T.: The Dubowitz syndrome. Further observations. Z. Kinderheilkd., *116*:1, 1973.



Above, Five month old showing short palpebral fissures, asymmetric ptosis, shallow supraorbital ridges, and mild micrognathia.

Below, Twenty month old showing eczema and above features; same patient at six and one half years of age at which time her I.Q. was 60.

(From Grosse, R., et al.: Z. Kinderheilkd., *110*:175, 1971. Courtesy of J. M. Opitz, Madison, Wisconsin.)

BLOOM SYNDROME

Short Stature, Malar Hypoplasia, Telangiectatic Erythema of the Face

Since Bloom's original description in 1954,[1] about 40 cases of this disorder have been reported.

ABNORMALITIES. Prenatal onset of shortness of stature. Facial telangiectatic erythema which involves the butterfly area and is exacerbated by exposure to sunlight usually develops in the first year of life. Café-au-lait spots. Variable microcephaly. Dolichocephaly, with malar hypoplasia, with or without a small nose.

OCCASIONAL ABNORMALITIES. Telangiectatic erythema of the dorsa of the hands and forearms. High-pitched voice; colloid-body–like spots in Bruch's membrane of the eye. Absence of upper lateral incisors. Prominent ears. Ichthyotic skin, hypertrichosis, pilonidal cyst, sacral dimple. Syndactyly, polydactyly, clinodactyly of fifth finger, short lower extremity, club foot. Immunoglobulin deficiency, most particularly of IgA and IgM. Propensity to develop lymphoreticular malignancy.

NATURAL HISTORY. These patients show a consistently slow pace of growth. Feeding problems are frequent during infancy. The facial erythema is very seldom present at birth, usually appearing during infancy following exposure to sunlight; it may excoriate, but improves after childhood. These are pleasant children with normal intelligence.

Malignancy has been the major known cause of death. Three patients are known to have died of leukemia, and another is reported to have a solid malignant tumor, out of 23 cases studied. Gastrointestinal malignancy is common after the age of 30.

Of interest is the in vitro tendency to chromosomal breakage and rearrangements found in cultured leukocytes and fibroblasts from all patients studied and, to a lesser extent, in some of their parents.

ETIOLOGY. Autosomal recessive, with the majority of individuals being of Ukrainian Jewish ancestry. The excess of affected males to females is unexplained.

COMMENT. The relation of the in vitro chromosomal breakage and the development of malignancies is not well understood at present. The same type of chromosomal breakage has been observed in Fanconi's pancytopenia syndrome, in which there is also an increased frequency of leukemia among affected individuals and close relatives.

REFERENCES

1. Bloom, D.: Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs. Am. J. Dis. Child., *88*:754, 1954.
2. Bloom, D.: The syndrome of congenital telangiectatic erythema and stunted growth. J. Pediatr., *68*:103, 1966.
3. Sawitsky, A., Bloom, D., and German, J.: Chromosomal breakage and acute leukemia in congenital telangiectatic erythema and stunted growth. Ann. Intern. Med., *65*:487, 1966.
4. German, J.: Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. Am. J. Hum. Genet., *21*:196, 1969.



Four and one half year old. Height age, two and one half years. Died of leukemia at 13 and one half years. (Courtesy of Dr. D. Bloom.)

DE SANCTIS–CACCHIONE SYNDROME

(Xerodermic Idiocy Syndrome)

Xeroderma Pigmentosa, Microcephaly, Hypogonadism

Only about 20 cases of this disorder have been reported since its initial recognition by De Sanctis and Cacchione[1] in 1932.

ABNORMALITIES[1–4]

Growth. Moderate to severe growth deficiency.

Central Nervous System. Microcephaly, mental deficiency, and deterioration with cerebral cortical and cerebellar "atrophy" and abnormal EEG. Variable spasticity, incoordination, seizures.

Skin. Undue sun sensitivity with progression from erythema and scaling to spotty hyperpigmentation, plus flat wart-like lesions and telangiectases, to epitheliomas and atrophy with contractures, to cutaneous malignancy.

Gonadal. Small testes in the male with variable hypogonadism in both sexes.

NATURAL HISTORY. Slow developmental progress and growth with variable neurologic dysfunction including seizures from early childhood. Progressive skin deterioration, especially related to exposure to the sun. Shortened life expectancy due to central nervous system deterioration and/or malignancy.

ETIOLOGY. Autosomal recessive. These patients have a defect in DNA repair as the presumed basis for the deterioration of the skin following exposure to ultraviolet light (sunlight).[5]

REFERENCES

1. De Sanctis, C., and Cacchione, A.: L'idiozia xerodermia. Riv. Sper. Freniatr., *56*:269, 1932.
2. Silberstein, A. G.: Xeroderma pigmentosum with mental deficiency. A report of two cases. Am. J. Dis. Child., *55*:784, 1938.
3. Reed, W. B., May, S. B., and Nickel, W. R.: Xeroderma pigmentosum with neurological complications. The de Sanctis-Cacchione syndrome. Arch. Dermatol., *91*:224, 1965.
4. Hokkanen, E., Iivanainen, M., and Waltimo, O.: Zu den neurologischen Manifestationen des Xeroderma pigmentosum. Dtsch. Z. Nervenheilkd., *196*:206, 1969.
5. Cleaver, J. E.: DNA damage and repair in light-sensitive human skin disease. J. Invest. Dermatol., *54*:181, 1970.



Girl showing microcephaly, malar hypoplasia, and xeroderma pigmentosa of skin. (Courtesy of S. Myhre, Rainier State Training School, Buckley, Washington.)

JOHANSON-BLIZZARD SYNDROME

Hypoplastic Alae Nasae, Hypothyroidism, Deafness

In 1971 Johanson and Blizzard[1] reported three cases of this disorder and found one from the past literature, interestingly in an individual with XXY syndrome.[2] This syndrome incorporates elements of ectodermal dysplasia with endocrine and exocrine insufficiency, plus growth and mental deficiency.

ABNORMALITIES. From three cases.

Growth. Prenatal onset growth deficiency.

Performance. Mental deficiency with I.Q. 35 and 47.

Craniofacial. Mild to moderate microcephaly. Midline posterior scalp defects, variable sparse hair. Hypoplastic to aplastic alae nasae. Hypoplastic deciduous teeth, absent permanent teeth.

Urorectal. Caliectasis to hydronephrosis. Imperforate anus. Vagina septate or double.

Endocrine. Primary hypothryoidism.

Exocrine. Pancreatic insufficiency with malabsorption.

OCCASIONAL ABNORMALITIES. One case each: strabismus, clitoromegaly, small nipples and absent areolae, radiolucent skull defects, abnormal EEG, rectovaginal fistula, single urogenital orifice.

NATURAL HISTORY. The degree of mental deficiency and general deficit in performance is such that two of the three patients have been insitutionalized. Hypothyroidism may progress in degree and is unusual in that the cholesterol is not elevated; possibly related to the concomitant malabsorption. Improvement in growth rate may occur with thyroid and pancreatin replacement therapy. However, the inadequate extent of catch-up growth implies a primary growth deficiency problem as well, as further implied by the prenatal onset of the growth deficiency.

ETIOLOGY. Unknown, sporadic.

REFERENCES

1. Johanson, A., and Blizzard, R.: A syndrome of congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. J. Pediatr., *79*:982, 1971.
2. Grand, R. J., Rosen, S. W., di Sant'Agnese, P. A., and Kirkham, W. R.: Unusual case of XXY Klinefelter's syndrome with pancreatic insufficiency, hypothyroidism, deafness, chronic lung disease, dwarfism and microcephaly. Am. J. Med., *41*:478, 1966.



Three affected children. (From Johanson, A., and Blizzard, R.: J. Pediatr., *79*:982, 1971.)

SECKEL SYNDROME

Severe Short Stature, Microcephaly, Prominent Nose

Reported by Mann and Russell[1] in 1959, this condition was extensively studied by Seckel in 1960.[2]

ABNORMALITIES

Growth. Prenatal onset of marked growth deficiency.

CNS. Mental deficiency.

Cranium. Microcephaly with premature synostosis.

Facies. Hypoplasia with prominent nose.

Auricle. Low-set, malformed, or both; especially lack of lobule.

Upper Extremities. Clinodactyly of fifth finger, simian crease, absence of some phalangeal epiphyses, hypoplasia of proximal radius.

Lower Extremities. Dislocation of hip, hypoplasia of proximal fibula, gap between first and second toes.

Thorax. Only 11 ribs.

Genitalia. Cryptorchidism (male).

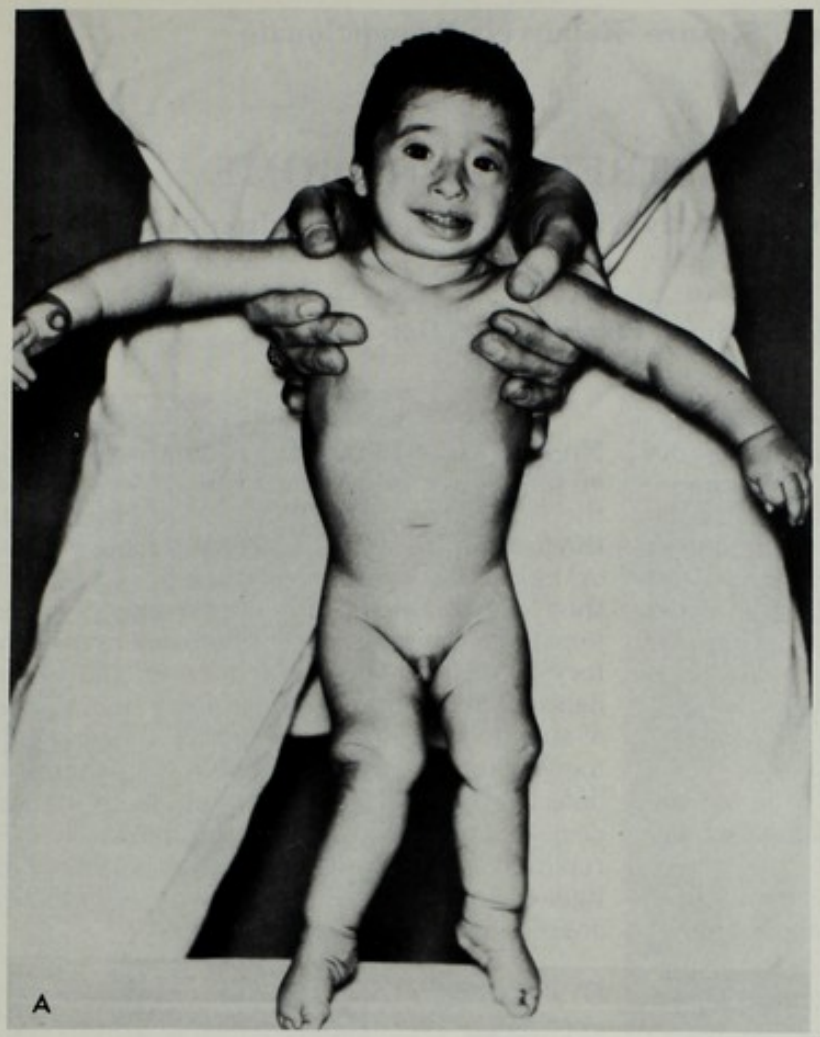
OCCASIONAL ABNORMALITIES. Facial asymmetry, strabismus, partial anodontia, enamel hypoplasia, sparse hair, scoliosis, club foot, pes planus, hypoplastic external genitalia.

NATURAL HISTORY. Gestational timing may be prolonged. Birth length, 13.5 to 17 inches; birth weight, 1 to 4.3 pounds. Final height, about 3 to 3½ feet. Moderate to severe mental deficiency, though early motor progress may be near normal. The cerebrum is small with a simple primitive convolutional pattern resembling that of a chimpanzee. Though they tend to be friendly and pleasant, these patients are often hyperkinetic and easily distracted. Poor joint development and support may be evident by dislocations of the hip, elbow, or both, and by later development of scoliosis, kyphosis, or both. Survival to an age of 75 years has been recorded.

ETIOLOGY. Probable autosomal recessive.

REFERENCES

1. Mann, T. P., and Russell, A.: Study of a microcephalic midget of extreme type. Proc. R. Soc. Med., *52*:1024, 1959.
2. Seckel, H. P. G.: Bird-Headed Dwarfs. Springfield, Ill., Charles C Thomas, 1960, p. 241.
3. Harper, R. G., Orti, E., and Baker, R. K.: Bird-headed dwarfs (Seckel's syndrome). A familial pattern of developmental, dental, skeletal, genital, and central nervous system anomalies. J. Pediatr., *70*:799, 1967.
4. McKusick, V. A., Mahloudji, M., Abbott, M. H., Lindenberg, R., and Kepan, D.: Seckel's bird-headed dwarfism. N. Engl. J. Med., *277*:279, 1967.







A, Fourteen month old; height age, two months. *B*, Five year old; height age, 19 months. (From Seckel, H. P. G.: Bird-Headed Dwarfs. Springfield, Ill., Charles C Thomas, 1960.)

C, Mentally deficient brother (six year old) and sister (three year old) with height ages of 11 months and four months respectively. (From Harper, R. G., et al.: J. Pediatr., *70*:799, 1967.)

HALLERMANN-STREIFF SYNDROME

(Oculomandibulodyscephaly with Hypotrichosis Syndrome)

Microphthalamia, Small Pinched Nose, Hypotrichosis

The first report was by Audry,[1] who described an incomplete case in 1893. Hallermann, in 1948, and Streiff, in 1950, independently described three cases, recognizing this syndrome as a separate entity. In 1958 Francois[2] collected all the previously published cases and emphasized the cardinal features of the condition. About 60 cases have been reported in the literature.

ABNORMALITIES

Growth. Proportionate small stature.

Craniofacial. Brachycephaly with frontal and parietal bossing, thin calvarium, and delayed ossification of the sutures.

Malar hypoplasia; micrognathia, with hypoplasia of the rami and anterior displacement of the temporomandibular joint.

Bilateral microphthalmia; congenital cataracts (26 of 27), total or incomplete, which may resorb spontaneously.

Nose thin, small, and pointed, with hypoplasia of the cartilage, becoming parrot-like with age.

Microstomia, narrow and high arched palate.

Dentition: hypoplasia of the teeth and/or malimplantation, neonatal teeth and partial anodontia.

Atrophy of the skin, most prominent over the nose and sutural areas of the scalp; thin and light hair, with hypotrichosis, especially of the scalp, eyebrows, and eyelashes.

OCCASIONAL ABNORMALITIES. Scaphocephaly, microcephaly, platybasia, shallow sella turcica, absence of the mandibular condyles, double cutaneous chin. Blue sclerae, nystagmus, strabismus, downward slant to palpebral fissures, optic disc coloboma, glaucoma and various chorioretinal pigment alterations. Syndactyly, winging of the scapulae, lordosis, scoliosis, spina bifida, funnel chest. Mental retardation. Hypogenitalism, cryptorchidism in the male.

NATURAL HISTORY. Because the majority of the literature pertains to the ocular defect, there are insufficient data upon which to base the natural history in terms of the growth defect or mortality in infants. During early infancy, they may have feeding and respiratory problems, even necessitating tracheostomy. Respiratory infections may contribute to the cause of death. The peculiar physiognomy and shortness of stature may impair their psychological adjustment, though the major handicap is the ocular defect, which usually culminates in blindness despite surgery. Though the majority of the reported patients have been of normal intelligence, motor and mental deficit, even to severe degree, have been reported.

ETIOLOGY. Until Guyard, et al.[4] reported an apparently affected father and daughter, the etiology was undetermined. Now the most likely hypothesis is that of a single mutant gene (dominant), most cases representing fresh mutations.

REFERENCES

1. Audry, C.: Variété d'alopécie congénitale; alopécie suturale. Ann. Dermat. et Syph. (Ser. 3), *4*:899, 1893.
2. Francois, J.: A new syndrome: dyscephalis with bird face and dental anomalies, nanism, hypotrichosis, cutaneous atrophy, microphthalmia and congenital cataract. Arch. Ophthalmol., *60*:842, 1958.
3. Hoefnagel, D., and Bernirschke, K.: Dyscephalia mandibulo-oculo-facialis. (Hallermann-Streiff syndrome). Arch. Dis. Child., *40*:57, 1965.
4. Guyard, M., Perdriel, G., and Ceruti, F.: Sur deux cas de syndrome dyscéphalizue à tête d'oiseau. Bull. Soc. Ophtalmol. Fr., *62*:443, 1962.
5. Judge, C., and Chalcanovskis, J. F.: The Hallermann-Streiff syndrome. J. Ment. Defic. Res., *15*: 115, 1971.



Left, Two and one half month old with height age of one month.
Right, Same patient at ten months showing changes in facies.
(From Smith, D. W.: J. Pediatr., *70*:481, 1967.)

ROTHMUND-THOMSON SYNDROME

(Poikiloderma Congenita Syndrome)

Development of Poikiloderma, Cataract with or without Other Ectodermal Dysplasia

This condition was first described in 1868 by Rothmund,[1] a Munich ophthalmologist who discovered multiple cases among an inbred group of people living in the nearby Alps. Over 25 cases have been reported.

ABNORMALITIES. Wide variance in expression, the most usual features being the following:

Skin. Irregular erythema progressing to telangiectasia, scarring, irregular pigmentation and depigmentation, atrophy.

Eyes. Juvenile zonular cataract (52 per cent), occasionally corneal dystrophy.

OCCASIONAL ABNORMALITIES

Skeletal. Small stature, small hands and feet, hypoplastic to absent thumbs, osteoporosis and/or areas of cystic or sclerotic change.

Facial. Small saddle nose.

Teeth. Microdontia and occasional anodontia.

Nails. Small, dystrophic.

Hair. Sparse, prematurely gray; occasionally alopecia.

Other Skin. Hyperkeratosis of palms and soles.

Other. Mental deficiency, hypogenitalism, hypogonadism.

NATURAL HISTORY. Changes in the skin are usually evident between three months and one year of age, and the progression toward irregular "marbled" hypoplasia, termed poikiloderma, is mainly noted in the first few years. Cataract most commonly becomes evident between two and seven years of age, and the principal problems for affected individuals are skin difficulties, sometimes photosensitivity; visual impairment requiring surgical intervention; and physical appearance, depending on the extent to which stature, hair, teeth, and/or nails are affected.

ETIOLOGY. Autosomal recessive with 70 per cent of affected individuals being female, an unexplained disparity which might not be of significance because the number of reported cases is small.

REFERENCES

1. Rothmund, A.: Ueber Cataracten in Verbindung mit einer eigenthümlichen Hautdegeneration. Arch. Ophthalmol., *14*:159, 1868.
2. Rook, A., Davis, R., and Stevanovic, D.: Poikiloderma congenitale. Rothmund-Thomson syndrome. Acta Derm. Venereol. (Stockh.), *39*:392, 1959.
3. Silver, H. K.: Rothmund-Thomson syndrome: an oculocutaneous disorder. Am. J. Dis. Child., *111*: 182, 1966.
4. Oates, R. K., Lewis, M. B., and Walker-Smith, J. A.: The Rothmund-Thomson syndrome. Aust. Paediatr. J., *7*:103, 1971.









A, Fifteen month old. (From Braun, W., and Unger, C.: Dermat. Wochenschr., *151*:1189, 1965.)

B, Two and one half year old. Note absence of lashes and mature cataract.

C, Patient shown in *B*. Note severe nail dysplasia. (*B* and *C* from Wahl, J. W., et al.: Am. J. Ophthalmol., *60*:722, 1965).

D, Five year old. (From Rook, A. J., et al.: Acta Derm. Venereol. (Stockh.), *39*:392, 1959.)

PROGERIA SYNDROME

(Hutchinson-Gilford Syndrome)

Alopecia, Atrophy of Subcutaneous Fat, Skeletal Hypoplasia and Dysplasia

The following entry was recorded in the *St. James Gazette* in 1754: "March 19, 1754 died in Glamorganshire of mere old age and a gradual decay of nature at seventeen years and two months, Hopkins Hopkins, the little Welshman, lately shown in London. He never weighed more than 17 pounds but for three years past no more than twelve."

In 1886 Hutchinson[1] described a similar patient. Later Gilford[2] studied this boy and another patient and termed the condition progeria, meaning premature aging. DeBusk[3] recently summarized the findings in 60 cases.

ABNORMALITIES

Alopecia. Onset birth to 18 months with degeneration of hair follicles.

Thin Skin. Onset early to mid-infancy.

Hypoplasia of Nails. Onset in infancy, nails may be brittle, curved, yellowish.

Loss of Subcutaneous Fat (Including Ear Lobule). Onset in infancy, last areas of adipose atrophy are cheeks and pubic area.

Periarticular Fibrosis. Onset at one to two years; stiff, or partially flexed prominent joints, or both; leads to "horse-riding" stance.

Skeletal Hypoplasia, Dysplasia, and Degeneration. Deficient growth, which becomes evident from six to 18 months; subsequent growth rate one-half to one-third normal. Facial hypoplasia with micrognathia, slim tubular bones and ribs with small thoracic cage, and thin calvarium with marked delay in ossification of fontanels. Skeletal dysplasia evident in coxa valga and tendency toward ovoid vertebral bodies; skeletal degeneration evident in loss of bone in clavicle and distal phalanges.

Dentition. Delayed eruption of deciduous and permanent dentition; crowding of teeth.

Atherosclerosis. As early as five years, onset of generalized atherosclerosis, especially evident in coronary arteries, aorta, and mesenteric arteries; at later age may have cardiac murmur, left ventricular hypertrophy.

Metabolic Alterations. Mild to moderate elevation of serum cholesterol.

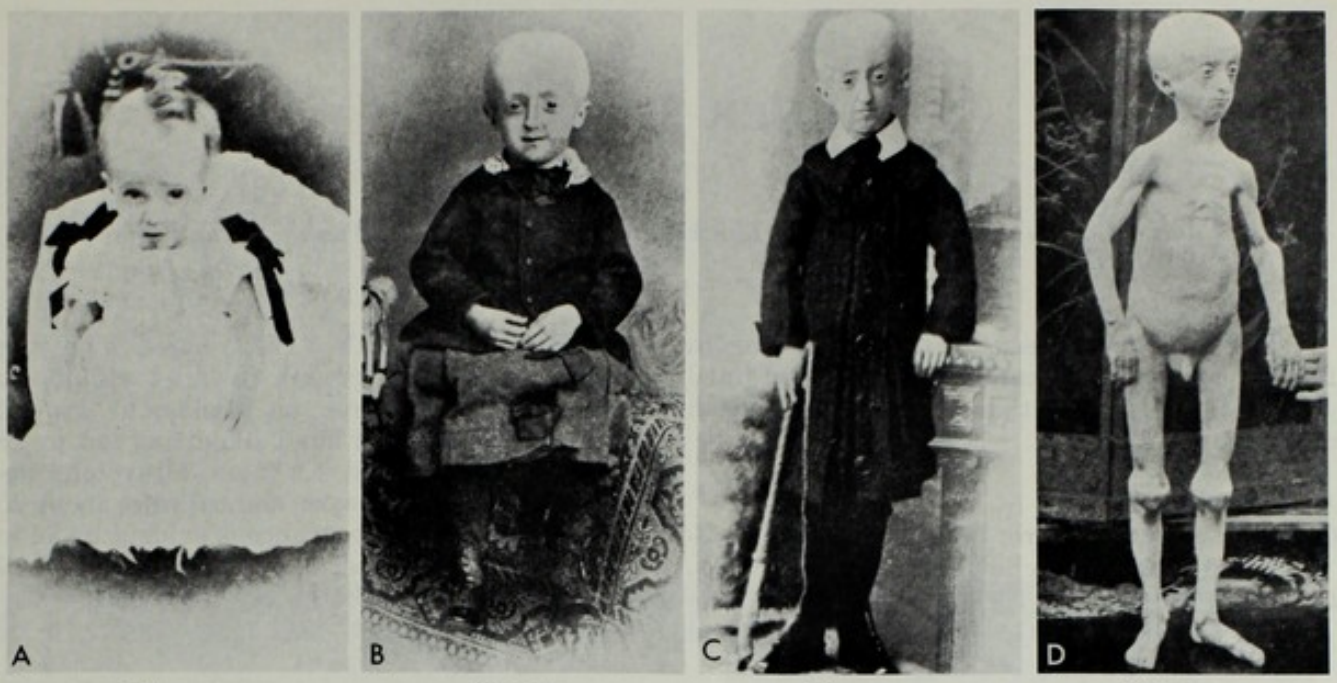
OCCASIONAL ABNORMALITIES. Scleroderma, irregular brownish-yellow skin pigmentation, perceptive hearing deficit, congenital or acquired cataract, absent breast and nipples, relatively large thymus and lymphoid and reticular hyperplasia, elevated serum lipoproteins, aminoaciduria.

NATURAL HISTORY. Though the onset of disease manifestations is usually stated as one to two years, there may be subtle indicators of disease within the first year. The average birth weight for 17 cases was 2.7 kg. One patient whose scalp was shaved at six weeks had no regrowth of hair. The deficit of growth becomes severe after one year of age. The tendency to fatigue easily is a factor that might limit full participation in childhood activities. The life span is shortened by the early advent of relentless arterial atheromatosis and the usual cause of death is coronary occlusion. The life expectancy for 13 cases was seven to 27 years with an average of 14.2 years. Since intelligence and brain development do not appear to be impaired, children with progeria should be allowed as normal a social life as possible.

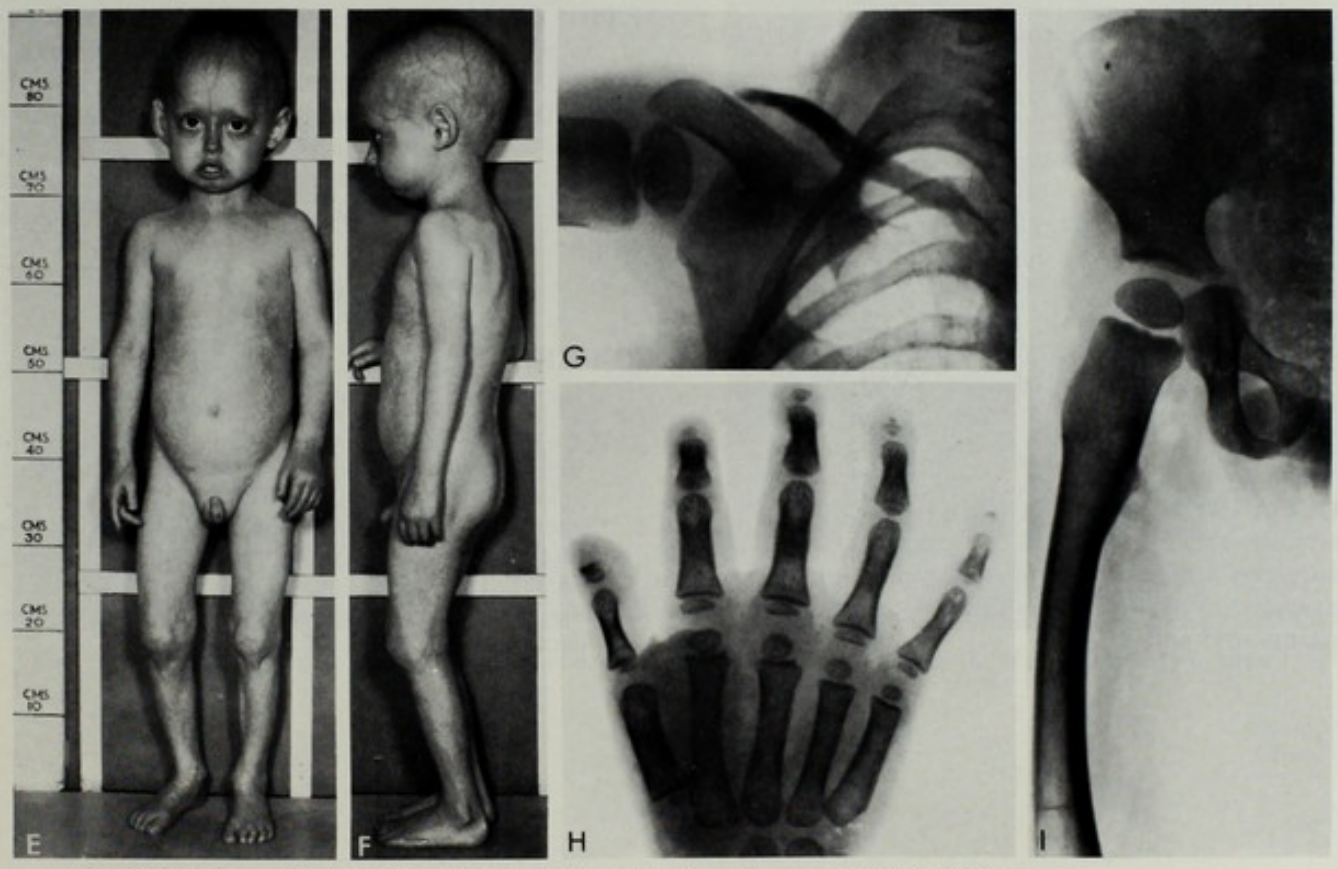
At the present time there is no effective therapy; however, the cosmetic use of a wig is recommended.

ETIOLOGY. Unknown. Most cases are sporadic and older mean paternal age[3] suggests the possibility of a fresh mutant gene etiology. There are one or possibly two instances of affected siblings from normal parentage, suggesting autosomal recessive inheritance. Possibly there is etiologic heterogeneity for this phenotype.

COMMENT. This condition might be classified as an abiotrophic disease since tissues that initially were fairly well developed have undergone hypoplastic, atrophic, or degenerative change. The clinical picture is different from the normal process of senile aging and the term progeria therefore seems inappropriate.



1½ years 7 years 12 years 17 years



A to *D*, Gilford's original patient. (From Gilford, H.: Practitioner, *73*:188, 1904.)

E to *I*, Three year old showing loss of outer clavicle, distal phalanges, and straight femur. (From Macleod, W.: Br. J. Radiol., *39*:224, 1966.)

REFERENCES

1. Hutchinson, J.: Congenital absence of hair and mammary glands with atrophic condition of the skin and its appendages in a boy whose mother had been almost wholly bald from alopecia areata from the age of six. Trans. Med. Chir. Soc. Edinburgh, *69*:473, 1886.
2. Gilford, H.: Progeria: a form of senilism. Practitioner, *73*:188, 1904.
3. DeBusk, F. L.: The Hutchinson-Gilford progeria syndrome. J. Pediatr., *80*:697, 1972.

WERNER SYNDROME

Early Adult—Cataract, Thin Skin with Thick Fibrous Subcutaneous Tissue, Gray Sparse Hair

The subject of Werner's doctoral thesis in 1904, this disease is usually not diagnosed until young adult life. More than 125 cases have been recorded.

ABNORMALITIES

Growth. Short stature; mean stature of affected males, 61 inches; females, 57.5 inches.

Deterioration. Loss of subcutaneous fat; slim spindly extremities with small hands and feet; pinched facies with beak nose.

Thick fibrous subcutaneous tissue with thin dermis.

Osteoporosis, atherosclerosis with calcification.

Muscle hypoplasia with patchy areas of fibrosis.

Gray sparse hair, premature balding.

Cataract, retinal degeneration.

Premature loss of teeth.

Hypogonadism, reduced fertility.

High pitched voice, fibrous thickening in submucosal tissues.

Liver atrophy.

Adult-type diabetes (44 per cent).

Mönckeberg sclerosis with organic brain syndrome.

OCCASIONAL ABNORMALITIES. Propensity toward malignancy (10 per cent), especially sarcoma. Mild hyperthyroidism. Adrenal atrophy. Valvular sclerosis. Hyperkeratosis of palms and soles.

NATURAL HISTORY. Often noted to be slim with a slow rate of growth in latter childhood, these individuals have no adolescent growth spurt and reach their final height at ten to 18 years, usually around 13 years. Gray hair develops at around 20 years, and cataract about 25 years, and old age appearance is evident by 30 to 40 years, with the mean age of survival being 47 years. Calcification occurs not only in the atheromatous vessels but in the thick subcutaneous tissues as well.

ETIOLOGY. Autosomal recessive. Epstein, et al. noted a decreased rate of cell division plus a limited total number of mitotic divisions per cell in cultured fibroblasts from a patient with Werner syndrome, thereby suggesting a basic defect in cell life capacity resulting in severe disease which resembles, but is not the same as, aging.

REFERENCES

1. Werner, O.: Uber Katarakt in Verbindung mit Sklerodermie. (Doctoral dissertation, Kiel University.) Kiel, Schmidt and Klaunig, 1904.
2. Epstein, C. J., Martin, G. M., Schultz, A. L., and Motulsky, A. G.: Werner's syndrome. Medicine, *45*:177, 1966.
3. Fleischmajer, R., and Nedwich, A.: Werner's syndrome. Am. J. Med., *54*:111, 1973.



Forty-eight year old woman with Werner syndrome. (From Epstein, C. J., et al.: Medicine, *45*:177, 1966.)

COCKAYNE SYNDROME

Senile-Like Changes Beginning in Infancy, Retinal Degeneration and Impaired Hearing, Photosensitivity of Thin Skin

Cockayne[1] reported this disorder in siblings in 1946. Subsequently more than 16 other cases have been documented.

ABNORMALITIES[1-5]

Growth. Growth deficiency with loss of adipose by mid to late infancy.

Performance. Mental deficiency with unsteady gait; sometimes tremor. Weakness with peripheral neuropathy.

Moderate perceptive deafness.

Craniofacial. Salt and pepper retinal pigmentation, optic atrophy.

Relatively small cranium with thick calvarium, loss of facial adipose with slender nose, moderately sunken eyes, and thin skin which is photosensitive. Carious teeth.

Skin. Photosensitive dermatitis.

Extremities. Cool hands and feet, sometimes cyanotic.

Mild to moderate joint limitation.

Trunk. Relatively short, with biconvex flattening of vertebrae and tendency toward dorsal kyphosis.

Other. Hepatomegaly. Ohno and Hirooka[4] discovered albuminuria with hyalinization of glomeruli, atrophy of tubules, and interstitial fibrosis in renal biopsies from three affected individuals.

OCCASIONAL ABNORMALITIES. Intracranial calcification, small sella turcica, cataract, nystagmus, cloudy cornea, decreased sweating and tearing, some "marble" epiphyses in digits, asymmetrical fingers, short second toes, infolding of iliac crest, cryptorchidism. Graying of sparse hair.

NATURAL HISTORY. Growth and development proceed at a more normal rate in early infancy, and it is not until two to four years of age that the pattern of defect is clearly evident. The personality and behavior tend to be similar to the normal for mental age, which is defective. Photosensitivity of skin may lead to problems on exposure to sunlight.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Cockayne, E. A.: Dwarfism with retinal atrophy and deafness. Arch. Dis. Child., *21*:52, 1946.
2. Neill, C. A., and Dingwall, M. M.: A syndrome resembling progeria: a review of two cases. Arch. Dis. Child., *25*:213, 1950.
3. MacDonald, W. B., Fitch, K. D., and Lewis, I. C.: Cockayne's syndrome. An heredo-familial disorder of growth and development. Pediatrics, *25*:997, 1960.
4. Ohno, T., and Hirooka, M.: Renal lesions in Cockayne's syndrome. Tohoku J. Exp. Med., *89*:151, 1966.



Left, Six and five sixths year old. Height age, 16 months. (From Windmiller, J.: Am. J. Dis. Child., *105*:204, 1963.)

Right, Fourteen and one half year old. Height age, three and one half years. Bone age, 16 years. (Courtesy of R. M. Blizzard. From Wilkins, L.: Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, 3rd ed. Springfield, Ill., Charles C Thomas, 1965.)

SMITH-LEMLI-OPITZ SYNDROME

Anteverted Nostrils and/or Ptosis of Eyelid, Syndactyly of Second and Third Toes, Hypospadias and Cryptorchidism in Male

Four patients with this disorder were described by Smith, et al.[1] in 1964, and subsequently at least 43 cases have been reported.

ABNORMALITIES

Growth. Moderately small at birth with subsequent failure to thrive.

Performance. Moderate to severe mental deficiency with variable altered muscle tone.

Craniofacial. Microcephaly with narrow frontal area, auricles slanted or low-set, ptosis of eyelids, inner epicanthic folds, strabismus, broad nasal tip with anteverted nostrils, broad maxillary secondary alveolar ridges, micrognathia.

Limb. Simian crease, high frequency of digital whorl dermal ridge patterning, syndactyly of second and third toes.

Genitalia. Male: cryptorchidism, hypospadias, mild to severe.

OCCASIONAL ABNORMALITIES

CNS. Seizures, abnormal EEG.

Facial. Cataract, cleft palate.

Limb. Flexed fingers, asymmetrically short finger(s), distal axial triradius, polydactyly, metatarsus adductus, vertical talus, dislocation of hip, dysplasia epiphysealis punctata.

Other. Cardiac anomaly, hypoplasia of thymus, pyloric stenosis, inguinal hernia, renal anomaly, deep sacral dimple, pit anterior to anus. Unusually blond hair.

NATURAL HISTORY. Many of these babies are born in a breech presentation. Feeding difficulty and vomiting have been frequent problems in early infancy, and 20 per cent of the patients have died during the first year. Death appeared related to pneumonia in most of them, one of whom had a hemorrhagic necrotizing pneumonia with varicella, suggesting an impaired immune response. Necropsy studies have shown serious defects in brain morphogenesis, including micrencephaly, hypoplasia of the frontal lobes, hypoplasia of cerebellum and brain stem, dilated ventricles, irregular gyral patterns, and irregular neuronal organization. Irritable behavior with shrill screaming may pose a problem during infancy. Muscle tone, which may be hypotonic in early infancy, tends to become hypertonic with time. The degree of mental deficiency is usually moderate to severe. Two adults described have had I.Q.'s in the 20's.

ETIOLOGY. Autosomal recessive. More than one sibling has been affected in 40 per cent of the families and there are two recorded instances of parental consanguinity. The higher reported frequency of affected males versus females may be related to the ascertainment bias of the genital anomaly.

REFERENCES

1. Smith, D. W., Lemli, L., and Opitz, J. M.: A newly recognized syndrome of multiple congenital anomalies. J. Pediat., *64*:210, 1964.
2. Gibson, R.: A case of the Smith-Lemli-Opitz syndrome of multiple congenital anomalies in association with dysplasia epiphysealis punctata. Can. Med. Ass. J., *92*:574, 1965.
3. Dallaire, L., and Fraser, F. C.: The syndrome of retardation with urogenital and skeletal anomalies in siblings. J. Pediatr., *69*:459, 1966.
4. Nevo, S., Benderly, A., Levy, J., and Katznelson, M. B.: Smith-Lemli-Opitz syndrome in an inbred family. Am. J. Dis. Child., *124*:431, 1972.
5. Garcia, C. A., McGarry, P. A., Boirol, M., and Duncan, C.: Neurological involvement in the Smith-Lemli-Opitz syndrome. Dev. Med. Child Neurol., *15*:48, 1973.



A to *D*: *A*, Young infant raised as female. *B*, Ten month old; height age, six months. *C*, Older infant. *D*, Five year old; height age, 18 months. Note ptosis, nasal configuration; and prominent lateral palatine ridges.

E, Lateral view of patient *A*. Note prominent midforehead (glabella), micrognathia.

F, Clenched hand (patient *A*), a variable feature.

G, Simian crease and distal palmar axial triradius (arrow).

H, Unusual appearance of syndactyly of the second and third toes in three of four patients.

(*B*, *C*, *D*, *G*, and *H* from Smith, D. W., et al.: J. Pediatr., *64*:210, 1964.)

OPITZ-FRIAS SYNDROME

Swallowing Difficulties, Hypospadias, Hypertelorism

This disorder was initially reported by Opitz, et al. in 1969.

ABNORMALITIES[1-3]

Functional. Swallowing problems with recurrent aspiration, +/− achalasia. Stridorous respiration, +/− wheezing. Weak, hoarse cry.

Craniofacial. Hypertelorism (mild to moderate), slight slant to palpebral fissures, slanted auricles, +/− prominent parietal and occipital regions.

Genitalia. Hypospadias, +/− bifid scrotum.

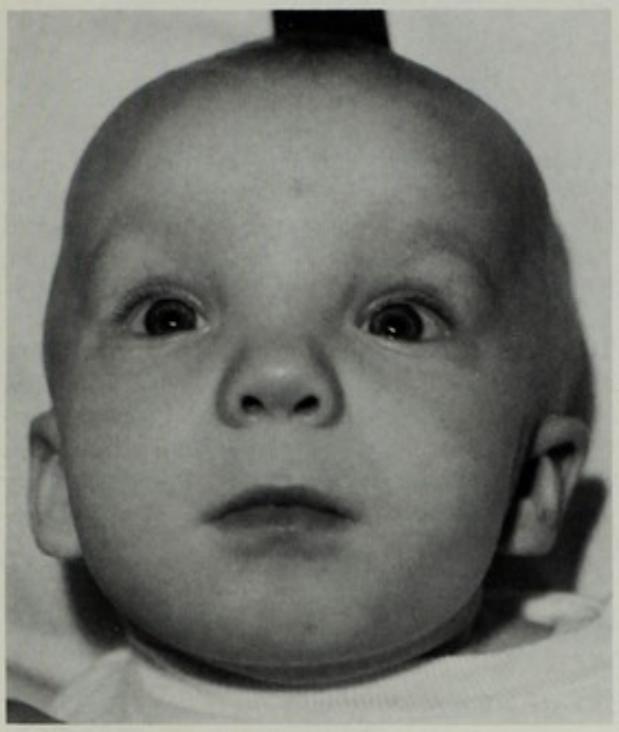
OCCASIONAL ABNORMALITIES. Short frenulum of tongue, lung hypoplasia, imperforate anus.

NATURAL HISTORY. Aspiration may be fatal and gastrostomy or jejunostomy should be seriously considered in affected males during early infancy. Survivors are usually of normal intelligence but may have continued respiratory problems.

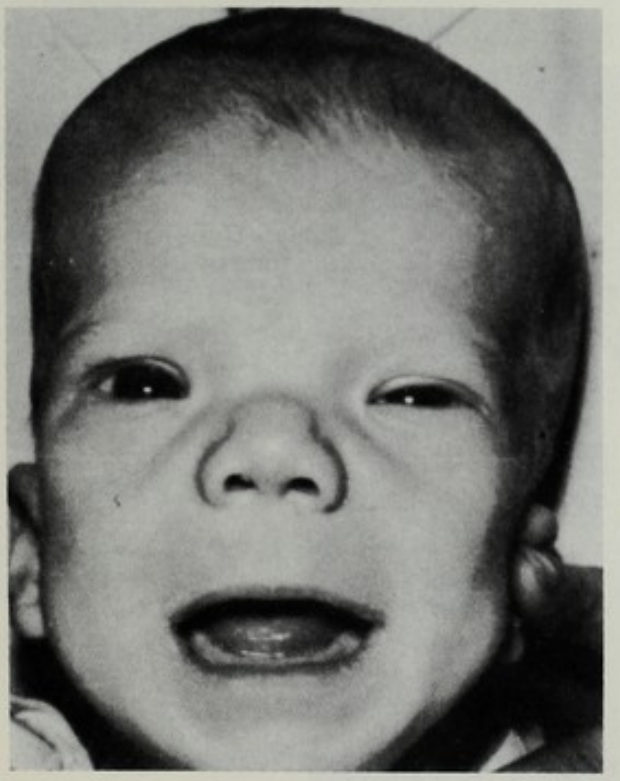
ETIOLOGY. Uncertain between X-linked (most likely) and autosomal dominant with partial sex limitation in expression. Partial features of the disorder have been noted in presumed carrier females, while affected males have had moderate to severe expression.

REFERENCES

1. Opitz, J. M., Frias, J. L., Gutenberger, J. E., and Pellett, J. R.: The *G* syndrome of multiple congenital anomalies. Birth Defects, *5*(2):95, 1969.
2. Coburn, T. P.: G syndrome. Am. J. Dis. Child., *120*:464, 1970.
3. Little, J. R., and Opitz, J. M.: The G syndrome. Am. J. Dis. Child., *121*:505, 1971.







Above, One month old.
Left, Seven and one-half month old. (From Opitz, J. M., et al.: Birth Defects, *5*(2):95, 1969.)

ROBINOW SYNDROME

(Fetal Face Syndrome)

Flat Facial Profile, Short Forearms, Hypoplastic Genitalia

Initially reported by Robinow, et al.[1] in 1969, at least 10 additional cases have been recognized.[2, 3]

ABNORMALITIES

Growth. Mild to moderate shortness of stature.

Craniofacial. Macrocephaly, large anterior fontanel, and frontal bossing with apparent hypertelorism, small upturned nose, long philtrum, and small mouth with micrognathia, hyperplastic alveolar ridges, and crowded teeth.

Limb. Short forearms with brachydactyly.

Spine. Hemivertebrae.

Genitalia. Small penis, clitoris, labia majora, cryptorchidism.

OCCASIONAL ABNORMALITIES

Oral-Facial. Nevus flammeus, epicanthal folds, posteriorly rotated ears, macroglossia, high arched palate, absent or bifid uvula.

Limb. Broad thumbs, toes, clinodactyly of fifth finger, hyperextensible fingers, short metacarpals, Madelung-like anomaly of forearm, and dislocation of hip.

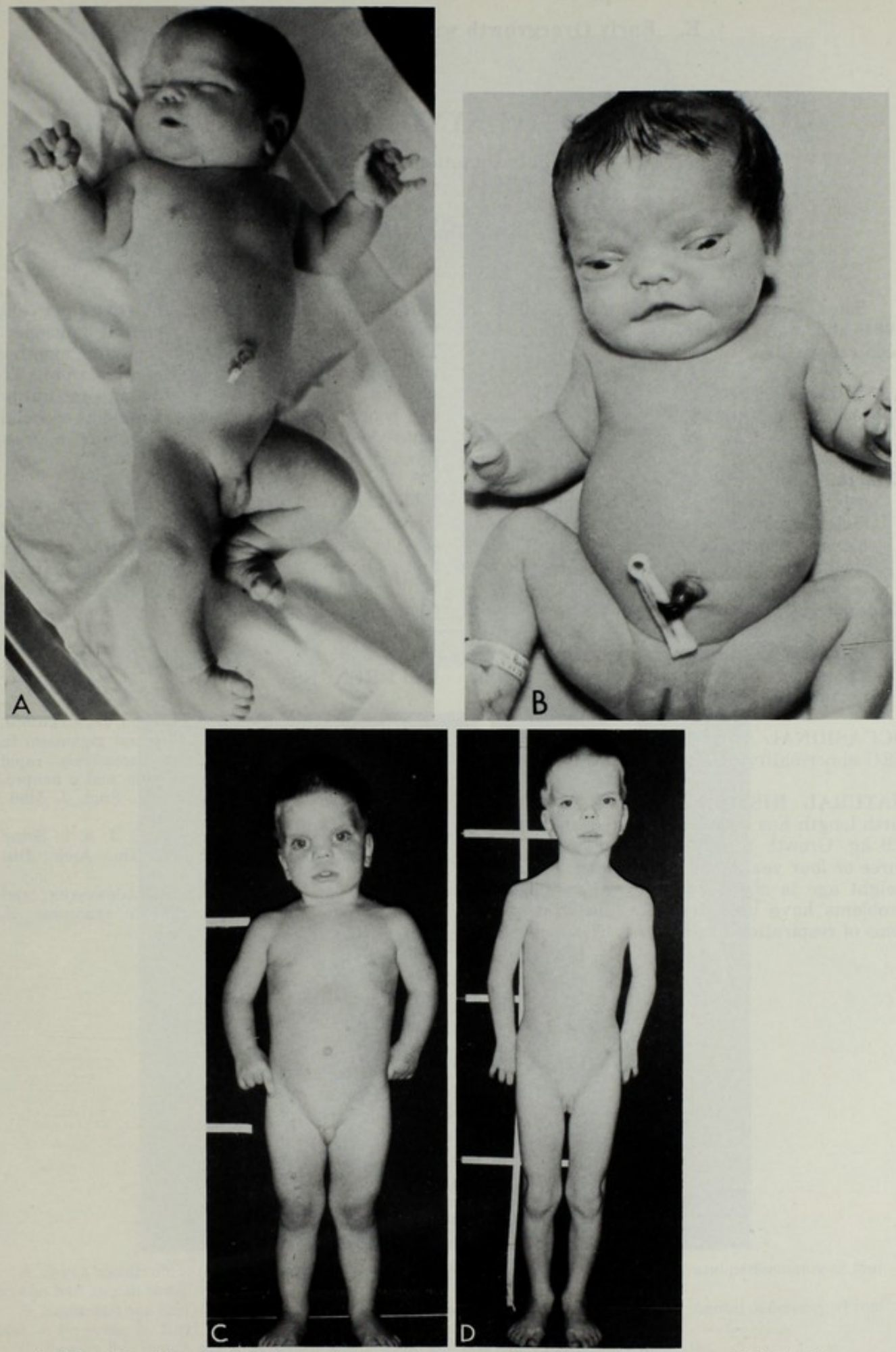
Other. Seizure, language deficiency, atrial septal defect, pectus excavatum, rib anomaly, inguinal hernia, and pilonidal dimple.

NATURAL HISTORY. The penile hypoplasia may be sufficient to initially raise the question of sex of rearing. Performance has been normal in most individuals. The one adult, a female, was 4 feet 10 inches in height.

ETIOLOGY. Autosomal dominant inheritance was implied in the family reported by Robinow, et al.[1] However, Wadlington, et al.[2] reported affected siblings of normal parents, and other cases have been sporadic in the family. The possibility of etiologic heterogeneity for this disorder remains open.

REFERENCES

1. Robinow, M., Silverman, F. N., and Smith, H. D.: A newly recognized dwarfing syndrome. Am. J. Dis. Child., *117*:645, 1969.
2. Wadlington, W. B., Tucker, V. L., and Schimke, R. N.: Mesomelic dwarfism with hemivertebrae and small genitalia (the Robinow syndrome). Am. J. Dis. Child., *126*:202, 1973.
3. Cohen, M. M., Jr., Needleman, H. L., and Cohen, M. M., Sr.: The fetal face syndrome. J. Pediatr., in press.



A, Three day old male with micropenis, hypertelorism, capillary hemangioma on central forehead.
B, Two day old female with flat facies, hypertelorism, minute clitoris.
C and *D*, Note small nose, hypertelorism, micropenis, and variable shortness of hands. (*A*, *C*, and *D* from Robinow, M., et al.: Am. J. Dis. Child., *117*:645, 1969. Copyright 1969, American Medical Association.)

SOTOS SYNDROME

(Cerebral Gigantism Syndrome)

Large Size, Large Hands and Feet, Poor Coordination

Sotos, et al.[1] described five such patients in 1964, and at least 80 cases have subsequently been reported.

ABNORMALITIES

Performance. Variable mental deficiency. I.Q.'s 18 to 119 with mean of 72. Poor coordination.

Growth. Prenatal onset of excessive size with relatively large span, and large hands and feet. Advanced osseous maturation, commensurate with height age. The phalangeal centers tend to be more accelerated than the carpal centers.

Craniofacial. Macrocephaly with prominent forehead (dolichocephalic). Downslanting palpebral fissures. Hypertelorism. Prognathism with narrow anterior mandible. High narrow palate. Coarse-looking facies.

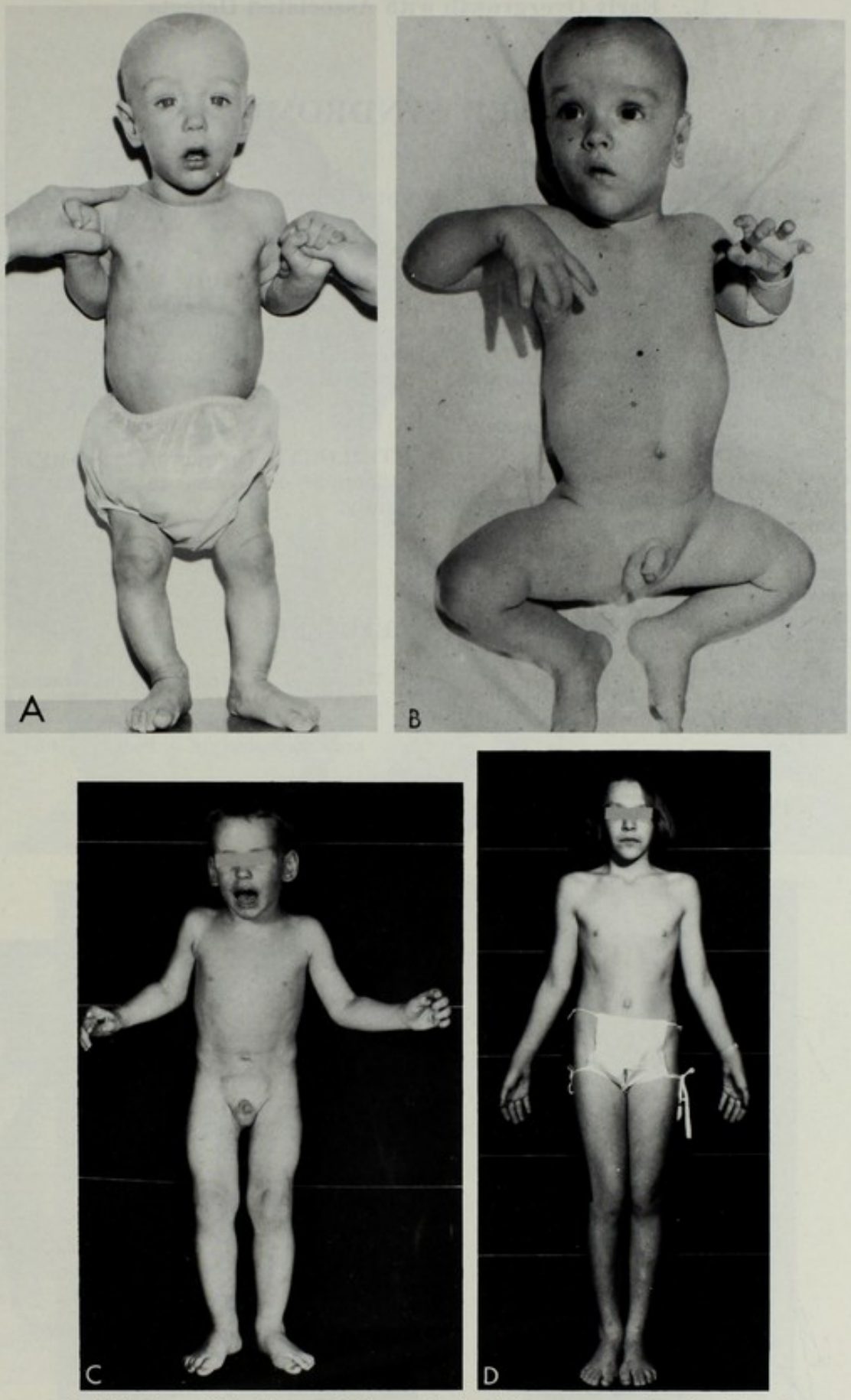
OCCASIONAL ABNORMALITIES. Seizures, EEG abnormality, strabismus, facial plethora.

NATURAL HISTORY. The mean full-term birth length has been 55.2 cm and birth weight 3.9 kg. Growth is especially rapid in the first three or four years, and at ten years of age the height age is about 14 or 15 years. Neonatal problems have been frequent, including problems of respiration and feeding. Thereafter general health has been good. Eighty-three per cent have had moderate to severe mental deficiency. The median age of sitting has been nine months; walking, 17 months; and saying a few words, 25 months. The excessive size with dull mentality and poor coordination leads to problems of social adjustment, occasionally with undue aggressiveness.

ETIOLOGY. Unknown. Sporadic, with occasional exception. The majority have been males (57 per cent). No consistent endocrine or other metabolic abnormality has been detected, and it is difficult to be certain whether all cases have a common etiology or not.

REFERENCES

1. Sotos, J. F., Dodge, P. R., Muirhead, D., Crawford, J. D., and Talbot, N. B.: Cerebral gigantism in childhood. A syndrome of excessively rapid growth with acromegalic features and a nonprogressive neurologic disorder. N. Engl. J. Med., *271*:109, 1964.
2. Abraham, J. M., and Snodgrass, G. J. A. I.: Sotos' syndrome of cerebral gigantism. Arch. Dis. Child., *44*:203, 1969.
3. Jaecken, J., van der Schueren-Lodeweyckx, and Eeckels, R.: Cerebral gigantism syndrome. Z. Kinderheilkd., *112*:332, 1972.



A, Seven month old infant with height age of 15 months, head size at two year level, and performance at four and one half month level.

B, Eight and one half month old infant with height age of 21 months and borderline mental deficiency. (From Sotos, J. F., et al.: N. Engl. J. Med., *271*:109, 1964.)

C, Twenty five month old with height age of three and one third years and I.Q. of 70.

D, Eleven year old with height of 5 feet, 8 inches and I.Q. of 70. (*B* and *C* are from Hook, E., and Reynolds, J. W.: J. Pediatr., *70*:900, 1967.)

WEAVER SYNDROME

Macrosomia, Accelerated Skeletal Maturation, Camptodactyly, Unusual Facies

Weaver, et al.[1] reported two strikingly similar boys with this pattern of overgrowth.

ABNORMALITIES. Two cases.

Growth. Accelerated growth and maturation, of prenatal onset.

Performance. Mild hypertonia, developmental lag, hoarse low-pitched cry.

Craniofacial. Large bifrontal diameter, flat occiput, ocular hypertelorism, large ears, long philtrum, relative micrognathia.

Limbs. Camptodactyly, broad thumbs, thin deep-set nails, prominent fingertip pads. Limited elbow and knee extension, clinodactyly of toes. Broad distal femurs and ulnae.

Other. Relatively loose skin, inverted nipples, thin hair. Umbilical hernia.

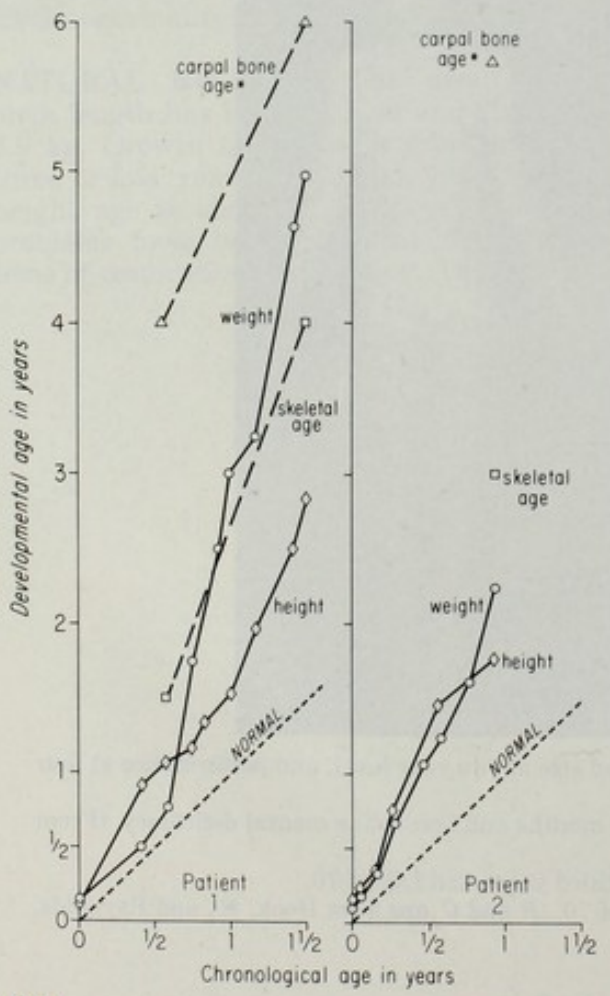
Anomalies Noted in Just One Patient. Inguinal hernia, talipes equinovarus, short fourth metatarsals.

NATURAL HISTORY. As noted in the growth chart, these children are large at birth and show accelerated growth and markedly advanced skeletal maturation during infancy. The natural history thereafter is unknown.

ETIOLOGY. Unknown. Each patient has been a sporadic occurrence in an otherwise normal family.

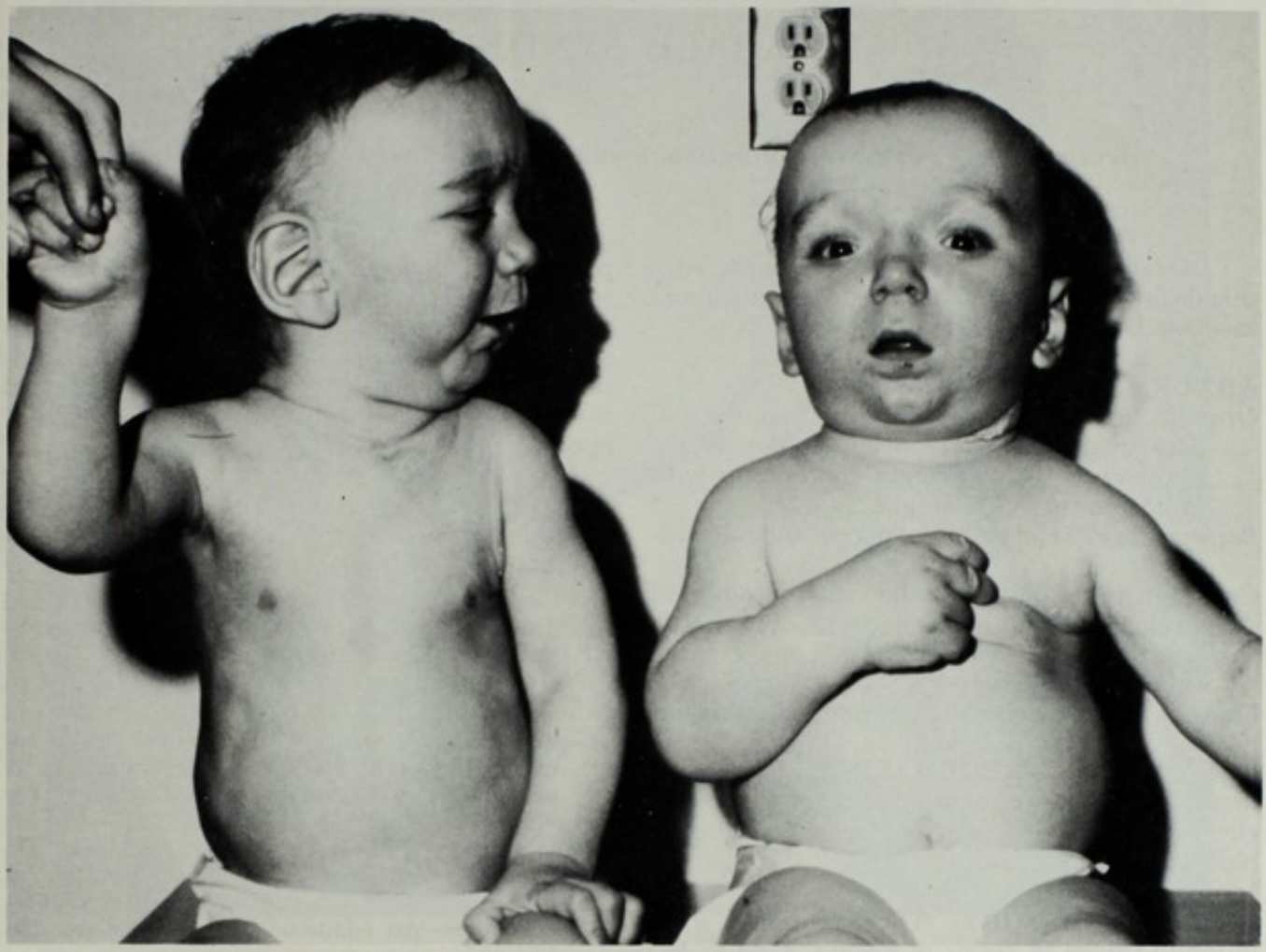
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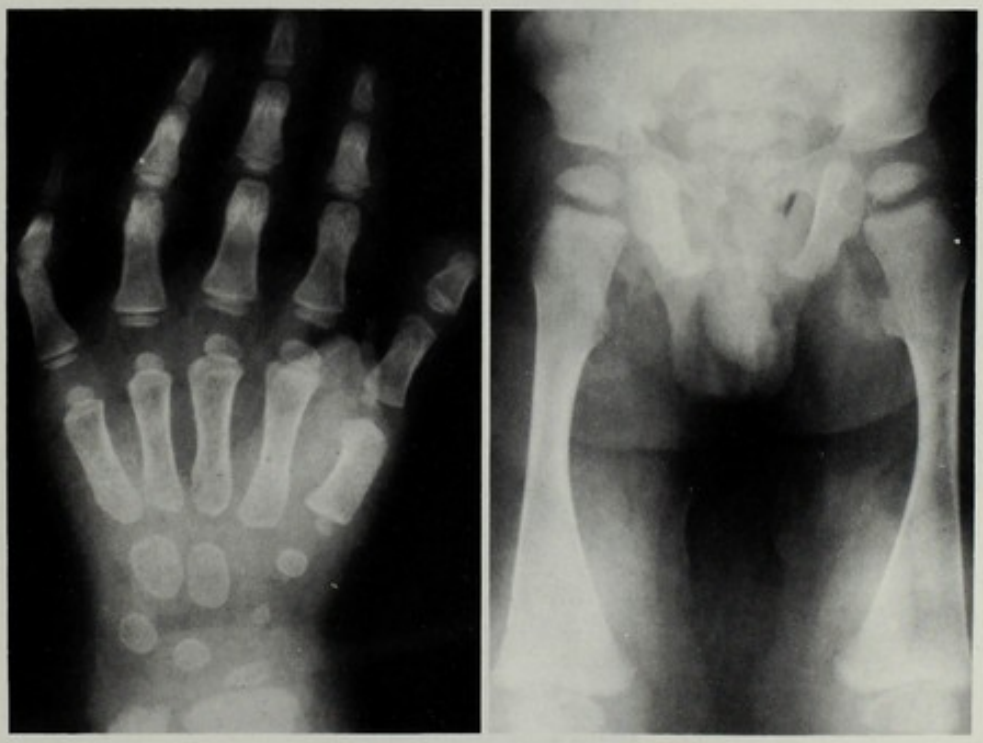
1. Weaver, D. D., Graham, C. B., Thomas, I. T., and Smith, D. W.: A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J. Pediatr., *84*:547, 1974.





Hand showing camptodactyly.
Accelerated growth and maturation in two patients.





Unrelated boys at 18 months and 11 months of age, respectively, and roentgenograms showing accelerated osseous maturation and broad distal splaying of femurs. (From Weaver, D. D., et al.: J. Pediatr., *84*:547, 1974.)

MARSHALL SYNDROME

Accelerated Growth and Maturation, Shallow Orbits, Broad Middle Phalanges

Marshall, et al.[1] reported two infants with this disorder in 1971 and at least one subsequent case has been recognized.[2]

ABNORMALITIES. Three cases.

Growth. Accelerated linear growth and markedly accelerated skeletal maturation of prenatal onset. Underweight for length, with failure to thrive in weight.

Performance. Motor and apparent mental deficiency.

Craniofacial. Long cranium with prominent forehead, shallow orbits with prominent eyes, bluish sclerae, upturned nose, small mandibular ramus.

Limbs. Broad proximal and middle phalanges.

OCCASIONAL ABNORMALITIES. One patient[2] had choanal atresia, rudimentary epiglottis, omphalocele, and a deep crease between hallux and second toe.

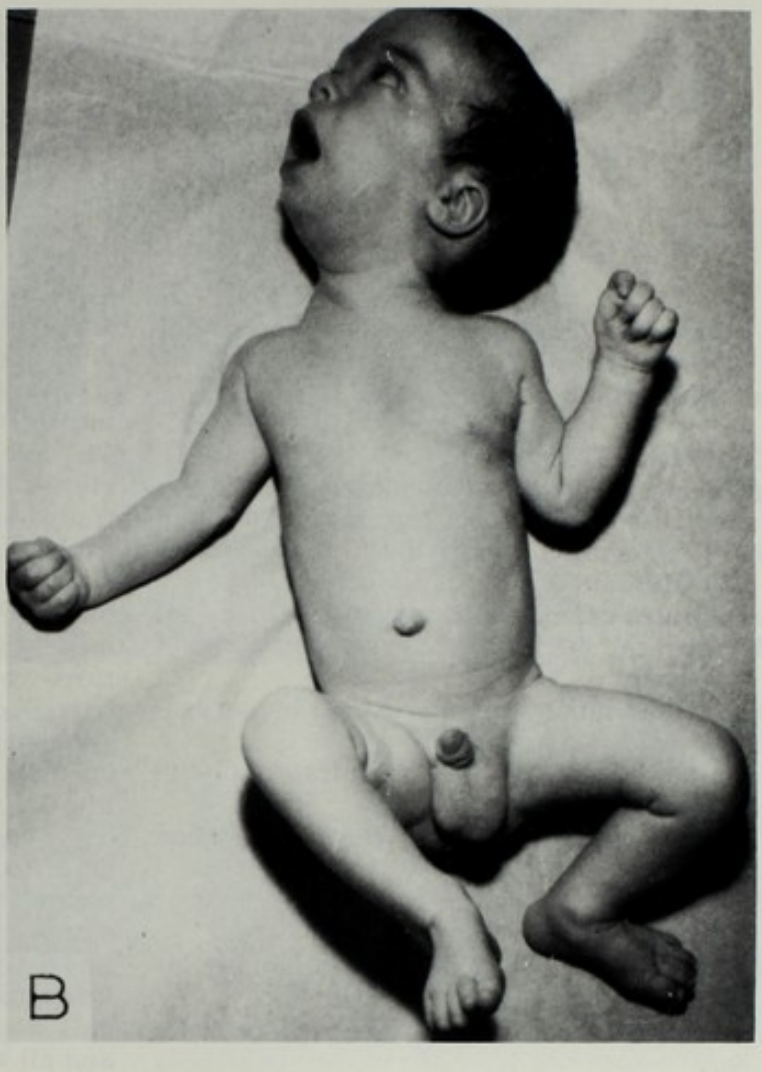
NATURAL HISTORY. These patients have failed to thrive in terms of weight, tend to hyperextend the head, have congestive problems with secretions, and have died with pneumonia at three to 20 months of age. The accelerated osseous maturation, of unknown cause, is of prenatal onset as indicated by a wrist "bone age" of three to four years in one patient at two weeks of age.[2]

ETIOLOGY. Unknown. The three affected males have each been a sporadic occurrence in the family.

REFERENCES

1. Marshall, R. E., Graham, C. B., Scott, C. R., and Smith, D. W.: Syndrome of accelerated skeletal maturation and relative failure to thrive: A newly recognized clinical growth disorder. J. Pediatr., *78*:95, 1971.
2. Visveshwara, N., Rudolph, N., and Dragutsky, D.: Syndrome of accelerated skeletal maturation in infancy, peculiar facies and multiple congenital anomalies—An additional case. J. Pediatr., *84*: 553, 1974.







A and *B*, Six and seven month old patients.

Left, Hand of one of them (patient A) at 16 months, showing a carpal bone age of six years and broad middle phalanges. (From Marshall, R. E., et al.: J. Pediatr., *78*:95, 1971.)

BECKWITH-WIEDEMANN SYNDROME

(Exomphalos-Macroglossia-Gigantism Syndrome)

Macroglossia, Omphalocele, Macrosomia, Ear Creases

Beckwith, et al. and Wiedemann reported this distinct clinical entity, and about 100 cases have subsequently been reported.

ABNORMALITIES

Performance. Unknown incidence of mild to moderate mental deficiency; may be normal.

Growth. Macrosomia with large muscle mass and thick subcutaneous tissue.
Accelerated osseous maturation.
Metaphyseal flaring with overconstriction of diaphyses.
Diminished tubulation of proximal humerus.

Craniofacial. Macroglossia.
Prominent eyes with *relative* infraorbital hypoplasia.
Capillary nevus flammeus, central forehead and eyelids.
Metopic ridge, central forehead.
Prominent occiput.
Malocclusion with tendency to mandibular prognathism.
Unusual linear fissures in lobule of external ear.
Linear indentations on posterior rim of helix.

Hyperplasia and Dysplasia. Large kidneys with renal medullary dysplasia.
Pancreatic hyperplasia, including excess of islets.
Fetal adrenocortical cytomegaly—*a consistent feature.*
Interstitial cell hyperplasia, gonads.
Pituitary amphophil hyperplasia.

Other. Neonatal polycythemia.
Hypoglycemia in early infancy (about one third to one half of cases).
Omphalocele or other umbilical anomaly.
Diastasis recti.
Posterior diaphragmatic eventration.
Cryptorchidism.

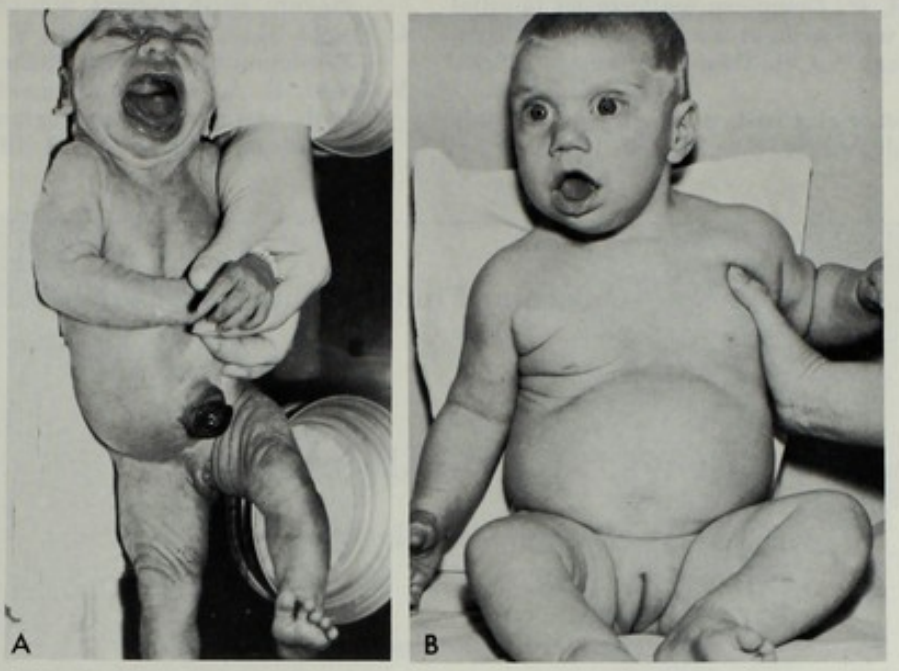
OCCASIONAL ABNORMALITIES. Hepatomegaly, mild microcephaly, hemihypertrophy, adrenal carcinoma, Wilms' tumor, gonadoblastoma, clitoromegaly, large ovaries, hyperplastic uterus and bladder, bicornuate uterus. Immunodeficiency.

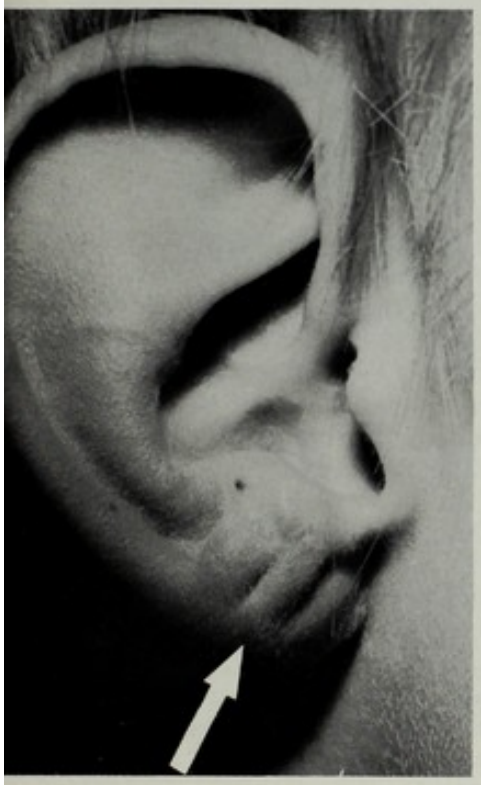
NATURAL HISTORY. Hydramnios and a relatively high incidence of prematurity provide further indication of the rather profound prenatal alterations. Birth weight has averaged 4 kg and length 52.6 cm. Severe problems of neonatal adaptation may occur, with apnea, cyanosis, and seizures as symptoms. Repair of an omphalocele is obviously indicated, but preoperative studies should be carried out to determine if the neonate has this syndrome, which accounted for at least 11.7 per cent of the cases of omphalocele reviewed by Irving. The large tongue may partially occlude respiration and lead to feeding difficulties. Placing the baby on its side or face down may help respiration, and a large soft nipple may facilitate feeding. Detection and treatment of hypoglycemia in any newborn with features of this syndrome are critical. The hypoglycemia is responsive to hydrocortisone analogue therapy, which is usually required for only one to four months. Polycythemia might also merit therapeutic intervention during the early neonatal period. Cautious follow-up for the detection of abdominal tumor is indicated, and pneumonia has been a frequent enough complication during infancy to warrant concern toward its early detection and treatment. All these measures are indicated because affected individuals who survive infancy generally are healthy, and all six (of 11) surviving children in Irving's study were considered mentally normal at four to eight and one-half years of age; however, Beckwith has noted mild to moderate mental deficiency in survivors.

Early postnatal growth may be slow, but thereafter macrosomia is the rule with growth around the ninetieth percentile and advanced skeletal maturation. Growth may allow adequate oral room for the large tongue. Partial glossectomy was performed in two of Irving's six surviving cases with good results. The prognosis beyond childhood is presently unknown.

ETIOLOGY. Unknown. Usually sporadic, with majority (60 per cent) being females. Three affected sibships. An occasional near relative may have the minor ear anomalies.

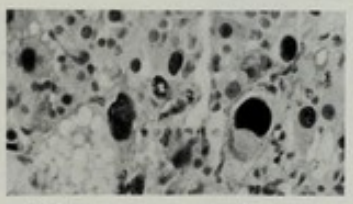
COMMENT. The search for the primary factor in the pathogenesis of this bizarre syndrome is of basic interest as well as of potential importance toward the treatment of these patients. Extensive endocrine and metabolic studies are indicated in individuals with this syndrome, especially looking for abnormal adrenocortical steroids in early infancy. The placenta should be studied and part of it frozen on any such patient, because no placental studies have yet been carried out in this disorder.

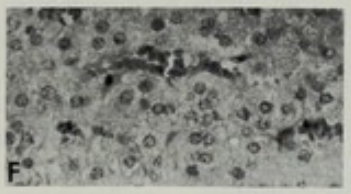


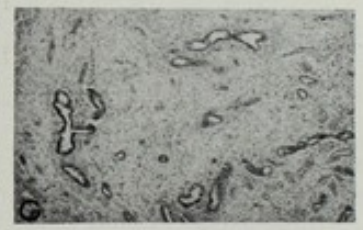














A, Newborn infant who became hypoglycemic. Note clitoromegaly.

B, Six month old large infant. Note scar of repaired omphalocele.

C, Unusual linear creases in the lobulus of the ear.

D and *E*, Kidney (*D*, left) and pancreas (*E*, lower) of patient compared to normal.

F and *G*, Fetal adrenal cytomegaly (above) compared to normal and renal medullary dysplasia *(G)*. (From Beckwith, J. B.)[3]

H, Similar facial appearance of five surviving children from four to eight years of age, who tend to be large for age with advanced skeletal maturation.

(C and *H* from Irving, I. M.: J. Pediatr. Surg., *2*:499, 1967.)

REFERENCES

1. Wiedemann, H. R.: Complexe malformatif familial avec hernie ombilicale et macroglossie—un "syndrome nouveau"? J. de Génét. Humaine, *13*:223, 1964.
2. Irving, I.: Exomphalos with macroglossia: A study of 11 cases. J. Pediatr. Surg., *2*:499, 1967.
3. Beckwith, J. B.: Macroglossia, omphalocele, adrenal cytomegaly, gigantism, and hyperplastic visceromegaly. Birth Defects, *5*(2):188, 1969.
4. Filippi, G., and McKusick, V. A.: The Beckwith-Wiedemann syndrome. Medicine, *49*:279, 1970.
5. Green, R. J., et al.: Immunodeficiency associated with exomphalos-macroglossia-gigantism syndrome. J. Pediatr., *82*:814, 1973.

F. Unusual Neuromuscular Findings with Associated Defects

MECKEL-GRUBER SYNDROME

(Dysencephalia Splanchnocystica)

Encephalocele, Polydactyly, Polycystic Kidney

Originally described by Meckel in 1822,[1] later by Gruber,[2] and more recently brought to recognition by Opitz and Howe,[3] more than 50 cases of this severe disorder have been reported.[4, 5]

ABNORMALITIES[3-5]

Growth. Variable prenatal growth deficiency.

CNS. Posterior or dorsal encephalocele. Microcephaly with sloping forehead, cerebral and cerebellar hypoplasia.

Facial. Microphthalmia. Cleft palate. Micrognathia. Ear anomalies, especially slanting.

Neck. Short neck.

Limbs. Polydactyly (usually postaxial), club feet.

Kidney. Polycystic, hypoplasia.

Genitalia. Cryptorchidism, incomplete development of external and/or internal genitalia.

OCCASIONAL ABNORMALITIES

Brain. Hydrocephalus, absent olfactory lobes, incomplete forebrain development, defects in basal and hypothalamic areas, absent pituitary.

Craniofacial. Craniosynostosis (possibly secondary). Coloboma of iris, hypotelorism or hypertelorism, hypoplastic to absent philtrum and/or nasal septum, cleft lip.

Mouth. Lobulated tongue, cleft epiglottis, neonatal teeth.

Neck. Webbed neck.

Limbs. Relatively short limbs, syndactyly, simian crease, clinodactyly.

Cardiac. Septal defect, patent ductus, coarctation of aorta, pulmonary stenosis.

Lung. Hypoplasia.

Liver. Bile duct proliferation fibrosis, cysts.

Other. Single umbilical artery, patent urachus, omphalocele, malrotation, accessory splenic tissue, adrenal hypoplasia, imperforate anus.

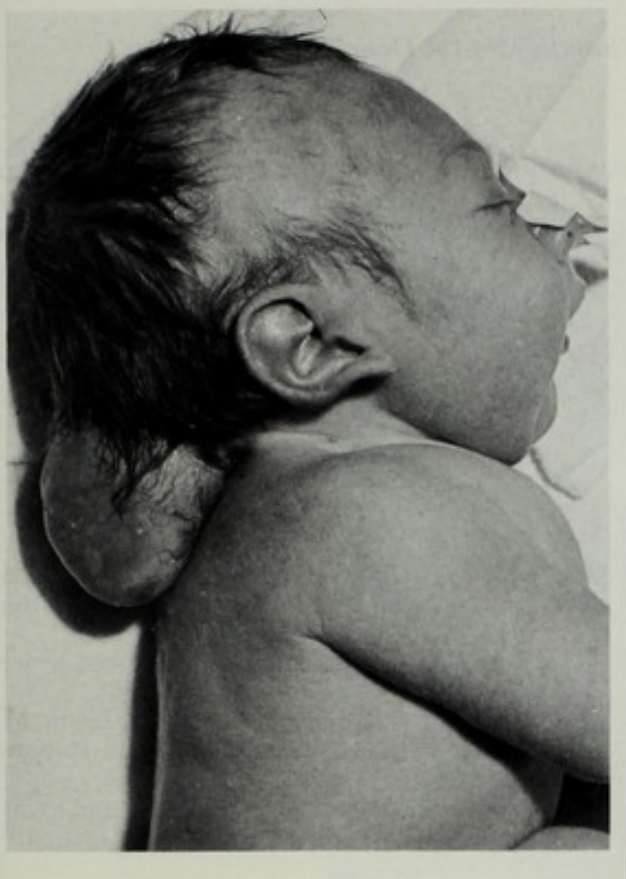
NATURAL HISTORY AND MANAGEMENT. These patients seldom survive more than a few days to weeks. Death may be related to the severe central nervous system defects and/or renal defect. Once the disorder is recognized, the parents should ideally be offered the option of no medical interference toward survival for babies with this syndrome.

COMMENT. Many of the more variable features within this syndrome may be secondary to early primary defects. For example, varying facial and brain components of the prechordal mesoderm type anomaly occur (arrhinencephaly, holoprosencephaly, etc.), as do anomalies secondary to incomplete renal development (Potter anomalad).

ETIOLOGY. Autosomal recessive, with no recognized expression in the presumed carriers of the gene.

REFERENCES

1. Meckel, J. R.: Beschreibung zweier durch sehr ahnliche Bildungsabweichung entsteller Geschwister. Dtsch. Arch. Physiol., *7*:99, 1822.
2. Gruber, G. B.: Beiträge zur Frage "gekoppelter" missbildungen (Akrocephalosyndactylie und Dysencephalia splanchnocystica). Beitr. Pathol. Anat., *93*:459, 1934.
3. Opitz, J. M., and Howe, J. J.: The Meckel syndrome







Two day old male with palpable enlarged kidney, who was having frequent seizures and other evidence of central nervous system abnormality. The polydactyly is usually postaxial, but was preaxial in this case. Intravenous pyelogram showed no visualization on one side and an aberrant calyceal system on the other side. The baby died at four and one half months of age, the oldest known survivor with this syndrome. Autopsy revealed polymicrogyria of the brain in addition to the posterior encephalocele with herniation of the cerebellum and brain stem, agenesis of the right kidney and Wolffian system, left pyelonephritis with abscesses, hypoplastic lung, and tracheal stenosis with complete tracheal rings. (Patient of E. Hatton, Anchorage, Alaska.)

(Dysencephalia splanchnocystica, the Gruber syndrome). Birth Defects, *5*:167, 1969.

4. Mecke, S., and Passarge, E.: Encephalocele, polycystic kidneys, and polydactyly as an autosomal recessive trait simulating certain other disorders: The Meckel syndrome. Ann. Genet. (Paris), *14*:97, 1971.
5. Hsia, Y. E., Bratu, M., and Herbordt, A.: Genetics of the Meckel syndrome (dysencephalia splanchnocystica). Pediatrics, *48*:237, 1971.

X-LINKED HYDROCEPHALUS SYNDROME

Hydrocephalus, Short Flexed Thumb, Mental Deficiency

Bickers and Adams[1] first described this entity in 1949, and subsequently at least 47 cases have been reported.

ABNORMALITIES

Performance. Mental deficiency and spasticity, especially of lower extremities.

Brain. Aqueductal stenosis with hydrocephalus.

Hand. Thumb flexed over palm (cortical thumb) with short first metacarpal.

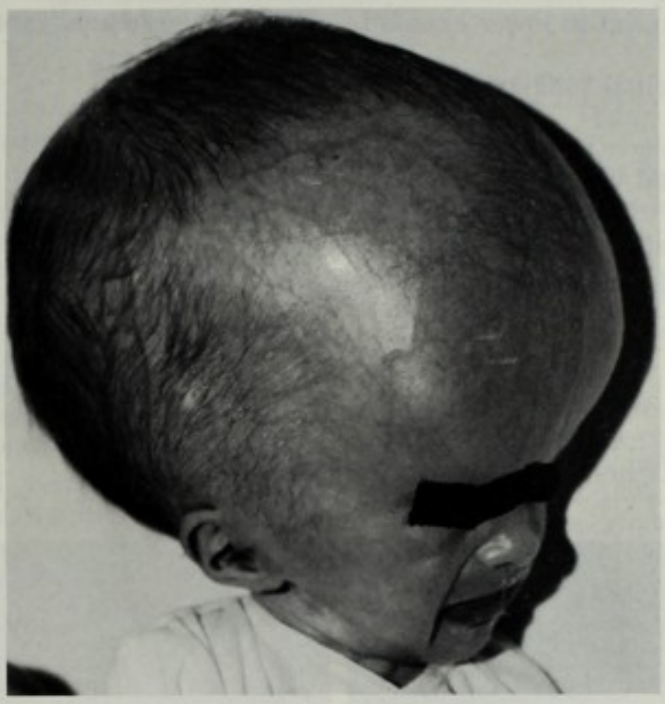
OCCASIONAL ABNORMALITIES. Asymmetry of somewhat coarse facies, brain defects such as fusion of thalami, small pons, absence of septum pellucidum, hypoplasia of corticospinal tracts, porencephalic cyst.

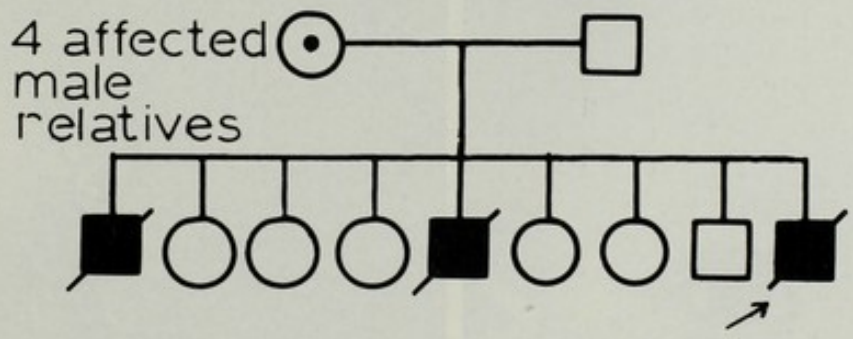
NATURAL HISTORY. Prenatal hydrocephalus may be severe enough to impede delivery. However, many of the affected males have no hydrocephalus, and such individuals often have a narrow scaphocephalic cranium with an intelligence quotient in the range of 30, and tend to have spasticity. The electroencephalogram may show diffuse abnormality, and the patient may have seizures.

ETIOLOGY. X-linked recessive. The carrier female may have dull intelligence.

REFERENCES

1. Bickers, D. S., and Adams, R. D.: Hereditary stenosis of the aqueduct of Sylvius as a cause of congenital hydrocephalus. Brain, *72*:246, 1949.
2. Edwards, J. H.: The syndrome of sex-linked hydrocephalus. Arch. Dis. Child., *36*:486, 1961.
3. Holmes, L. B., Nash, A., ZuRhein, G. M., Levin, M., and Opitz, J. M.: X-linked aqueductal stenosis. Pediatrics, *51*:697, 1973.
4. Fried, K.: X-linked mental retardation and/or hydrocephalus. Clin. Genet., *3*:258, 1973.





Male infant who later died and who was shown to have aqueductal stenosis as the cause for hydrocephalus. Note the family pedigree showing other affected males for whom this X-linked condition was lethal. (Courtesy of J. M. Opitz, University of Wisconsin.)

SJÖGREN-LARSSON SYNDROME

Ichthyosis, Mental Deficiency, Spasticity

Sjögren and Larsson[1] reported this entity in 28 Swedish individuals in 1957, and others with the same condition have been recognized subsequently.[2, 3]

ABNORMALITIES

Central Nervous System. Mental retardation; I.Q., 30 to 60 or less.
Spasticity, most pronounced in lower extremities.
Skin. Ichthyosis. Hair brittle and sparse.
Growth. Short stature.

OCCASIONAL ABNORMALITIES. Pigmentary retinal degeneration (30 per cent), seizures, diminished sweating except face and dorsum of hands, hypoplasia of teeth, enamel hypoplasia, hypertelorism, kyphosis. Metaphyseal dysplasia with small irregular epiphyses.

NATURAL HISTORY. Erythema of skin in early infancy with scaling and hyperkeratosis in most areas except face. Lichenification with exaggerated skin markings most evident in axillae and folds of neck. The mental defect usually includes speech problems of dysarthria, monosyllables, or no speech. The electroencephalogram may show slow paroxysmal activity.

ETIOLOGY. Autosomal recessive. Sjögren and Larsson tentatively traced all the Swedish cases back to one heterozygote 600 years ago.

REFERENCES

1. Sjögren, T., and Larsson, T.: Oligophrenia in combination with congenital ichthyosis and spastic disorders. Acta Psychiatr. Scand., *32*(Suppl. 113):1, 1957.
2. Selmanowitz, V. J., and Porter, M. J.: The Sjögren-Larsson syndrome. Am. J. Med., *42*:412, 1967.
3. Ozonoff, M. B., and Ogden, J. A.: Sjögren-Larsson syndrome with epiphyseal-metaphyseal dysplasia. Am. J. Roentgenol. Radium Ther. Nucl. Med., *118*:187, 1973.





A, Six year old. Note slight changes in skin and spacing of teeth.
B, Fourteen year old, showing thickened, ridged skin in axillary area.
(From Selmanowitz, V. J., and Porter, M. J.: Am. J. Med., *42*:412, 1967.)

MARINESCO-SJÖGREN SYNDROME

Cerebellar Ataxia, Hypotonia, Cataracts

This condition was described by Marinesco, et al.[1] in 1931 and further delineated by Sjögren[2] in 1947. Only about 50 cases have been reported.

ABNORMALITIES[1-4]

Growth. Mild to moderate growth deficiency.
Performance. Moderate to severe mental deficiency with cerebellar ataxia, weakness with or without hypotonia, and tendency toward nystagmus and dysarthria.
Eye. Cataracts, usually evident from early life.

OCCASIONAL ABNORMALITIES. Strabismus, development of kyphoscoliosis.

ETIOLOGY. Autosomal recessive with high incidence of parental consanguinity.

COMMENT. Todorov's pathological studies indicated a degenerative process, most severe in the cortical areas of the cerebellum.[4]

REFERENCES

1. Marinesco, G., Draganesco, S., and Vasiliu, D.: Nouvelle maladie familiale caracterisé par une cataracte congénitale et un arrêt du développement somato-neuro-psychique. Encephale, *26*:97, 1931.
2. Sjögren, T.: Hereditary congenital spinocerebellar ataxia combined with congenital cataract and oligophrenia. Acta Psychiatr. Scand. Suppl., *46*:286, 1947.
3. Andersen, B.: Marinesco-Sjögren syndrome: spinocerebellar ataxia, congenital cataract, somatic and mental retardation. Dev. Med. Child. Neurol., *7*:249, 1965.
4. Todorov, A.: Le syndrome de Marinesco-Sjögren. Première étude anatomo-clinique. J. Genet. Hum., *14*:197, 1965.

ATAXIA-TELANGIECTASIA SYNDROME

(Louis-Bar Syndrome)

Ataxia, Telangiectasia, Lymphopenia, and Immune Deficit

Though this disease was initially described by Louis-Bar in 1941, it has only recently received broader recognition, with well over 100 cases having been reported since 1958.

ABNORMALITIES

Growth. Deficiency, variable in age of onset.

CNS. Progressive ataxia and other evidence of degeneration of CNS function, including mental deficiency and posterior column dysfunction.

Skin and Conjunctiva. Telangiectasia in bulbar conjunctiva and later over bridge of nose, auricles, elsewhere.

Respiratory. Catarrh, frequent respiratory infections; bronchiectasis may develop.

Immune System. Deficiency in cellular immunity with thymic hypoplasia, hypoplasia of tonsil and adenoid lymphoid tissue, lymphopenia, and often low to absent gamma IgA and IgE globulins.

OCCASIONAL FEATURES

Skin and Hair. Areas of altered skin or hair pigmentation, including café-au-lait spots. Sclerodermatous changes.

Lymphoreticular System. Malignancy, including leukemia, sarcoma, and Hodgkin's disease, in about 10 per cent of patients.

Gonad. Sexual immaturity. Ovarian dysgerminoma or hypoplasia.

NATURAL HISTORY. Growth deficiency, though it may be prenatal in onset, more commonly becomes evident in latter infancy or in childhood. Progressive ataxia usually develops during infancy and is usually accompanied by features of choreoathetosis, and by dysrhythmic speech, drooling, aberrant ocular movements such as fixation nystagmus, a stooped posture plus dull sad facies, and occasionally seizures. Instability, suggesting vestibular deficit, often becomes so severe that ambulation is no longer possible in later childhood. These children are usually affable and pleasant despite their progressive handicap. Mental deficiency, though difficult to assess, is considered a feature in about 50 per cent of cases, especially in later stages of this fatal disease. The immune deficiency probably contributes to the frequent respiratory infections and bronchiectasis; however, the persistent catarrh and the progressive generalized bronchiectasis are relatively unresponsive to antibiotic management, and there may be a basic problem in the mucous membranes besides the cellular immune deficit. Death is usually a consequence of lung infection, neurologic deficit, or both. Affected patients seldom survive later childhood. The oldest survivor was 37 years old and the disease had been quiescent for 20 years.

ETIOLOGY. Autosomal recessive.

COMMENT. The general hypoplasia of the whole individual and immune deficit with abiotrophic features of deterioration in the central nervous system, skin, and respiratory tract indicate the severe pleiotrophic effect of this pair of mutant genes. No common cellular metabolic defect has yet been detected; however, it is of interest to note certain common features between Fanconi's syndrome, Bloom's syndrome, and ataxia-telangiectasia. In each of these disorders there is generalized growth deficiency, skin disorder, and a propensity to develop lymphoreticular malignancy, plus a high frequency of chromosomal breakage in cultured leukocytes.

REFERENCES

1. Louis-Bar, D.: Sur un syndrome progressif comprenant des télangiectasies capillaires cutanées et conjonctivales, à disposition naevoïde et des troubles cérébelleux. Confin. Neurol., *4*:32, 1941.
2. McFarlin, D. W., Strober, W., and Waldmann, T. A.: Ataxia telangiectasia. Medicine, *51*:281, 1972.



Nine and one half year old. Height age, eight years. (From Smith, D. W.: J. Pediatr., *70*:487, 1967.)

MENKES SYNDROME

(Menkes Kinky Hair Syndrome)

Progressive Cerebral Deterioration with Seizures, Twisted and Fractured Hair

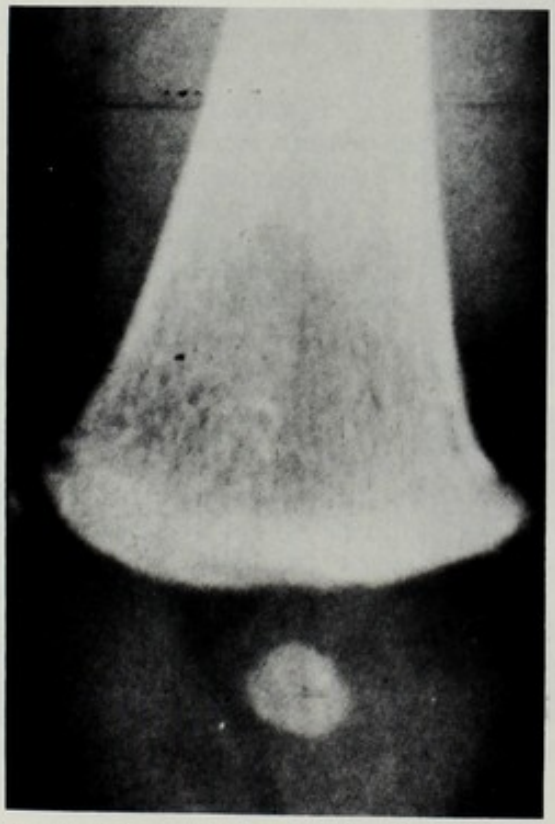
Menkes et al.[1] described five related male infants with this disease in 1962, and Danks, et al.[2, 3] have subsequently indicated that all features of the disorder are the result of copper deficiency.

ABNORMALITIES

Growth. Deficiency, sometimes small at birth.

Central Nervous System. Severe degenerative process in cerebral cortex with gliosis and atrophy. Profound and progressive neurological deficit from one to two months with hypertonia, irritability, seizures, intracranial hemorrhage, hypothermia, and feeding difficulties.

Facies. Lack of expressive movement, pudgy cheeks.



Irregular trabecular patterning in distal femoral metaphysis with fragmentation.

Hair. Sparse, stubby and lightly pigmented, which shows twisting and partial breakage by magnified inspection.

Skin. Occasionally thick and relatively dry.

Skeletal. Wormian bones, metaphyseal widening, particularly of ribs and femur, with formation of lateral spurs which frequently fracture.

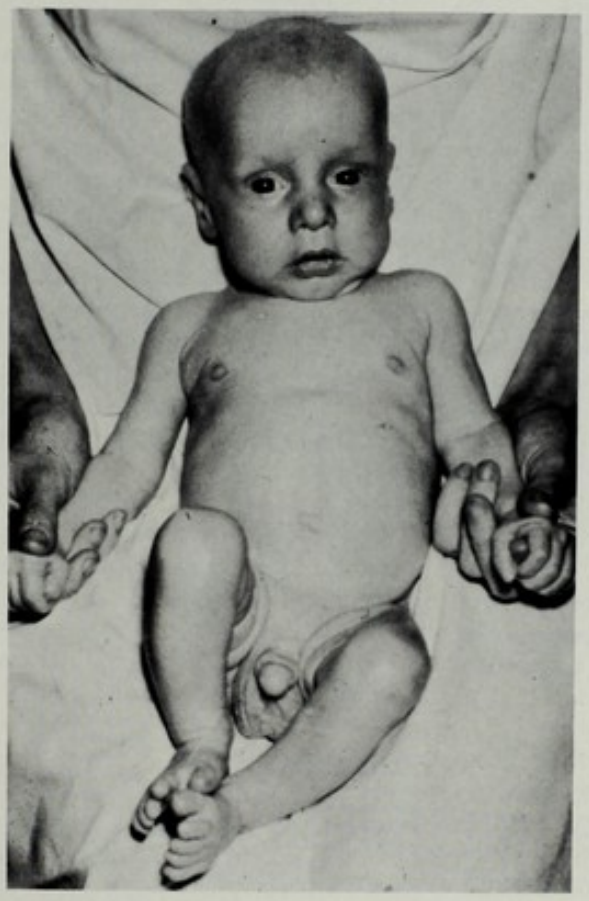
COMMENT. Arteriograms, as well as necropsy material, have shown widespread arterial elongation and tortuosity, most likely due to deficiency of copper dependent cross-linking in the internal elastic membrane of the arterial wall. Many of the CNS degenerative changes as well as the skeletal changes are due to ischemia secondary to the arterial abnormalities.

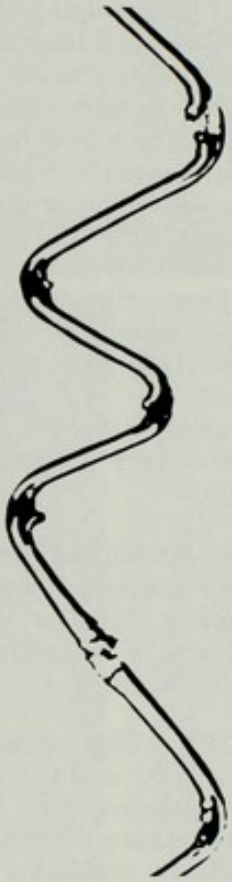
NATURAL HISTORY. Progressive deterioration beginning in early infancy with death in infancy or as late as three years. Hair is normal at birth but by six weeks begins to lose pigmentation. The skeletal changes have been confused with those occurring in the Battered Child syndrome. Danks, et al.[2] have demonstrated a defect in intestinal copper absorption such that low levels of serum copper and ceruloplasmin have been found in all patients studied. Parenteral administration of copper has not been successful in reversing the clinical features.

ETIOLOGY. X-linked recessive.

REFERENCES

1. Menkes, J. H., Alter, M., Steigler, G. K., Weakley, D. R., and Sung, J. H.: A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. Pediatrics, *29*:764, 1962.
2. Danks, D. M., Stevens, B. J., Campbell, P. E., et al.: Menkes' kinky hair syndrome. Lancet, *1*:1100, 1972.
3. Danks, D. M., Campbell, P. E., Stevens, B. J., et al.: Menkes' kinky hair syndrome. An inherited defect in copper absorption with widespread effects. Pediatrics, *50*:188, 1972.





2 months – 2.6 kg. Scalp hair × 100

(From Menkes, J. H., et al.: Pediatrics, *29*:764, 1962.)

PRADER-WILLI SYNDROME

Hypotonia, Obesity, Small Hands and Feet

Prader, Labhart, and Willi[1] reported this pattern of abnormality in nine children in 1956, and subsequently over 200 cases have been recorded.

ABNORMALITIES

Small Stature. May be small at birth, occasionally normal stature until later childhood.

Obesity. Onset from infancy to six years.

Craniofacial. Almond-shaped appearance to palpebral fissures which may be upslanting. Narrow bifrontal diameter. Strabismus.

Mental Deficiency. Intelligence quotient 20 to 80, most commonly 40 to 60.

Hypotonia. Severe in early infancy.

Small Hands and Feet. Slowing in growth of hands and/or feet, usually becoming evident in midchildhood. One patient wore size 3 shoes at 23 years.

Small Penis and Cryptorchidism. Frequent hypogonadism, secondary to hypogonadotropism.

OCCASIONAL ABNORMALITIES. Poor fine and gross motor coordination. Upsweep of frontal scalp. Microcephaly, seizures, clinodactyly, syndactyly, hypoplasia of auricular cartilage. Diabetes mellitus. Scoliosis.

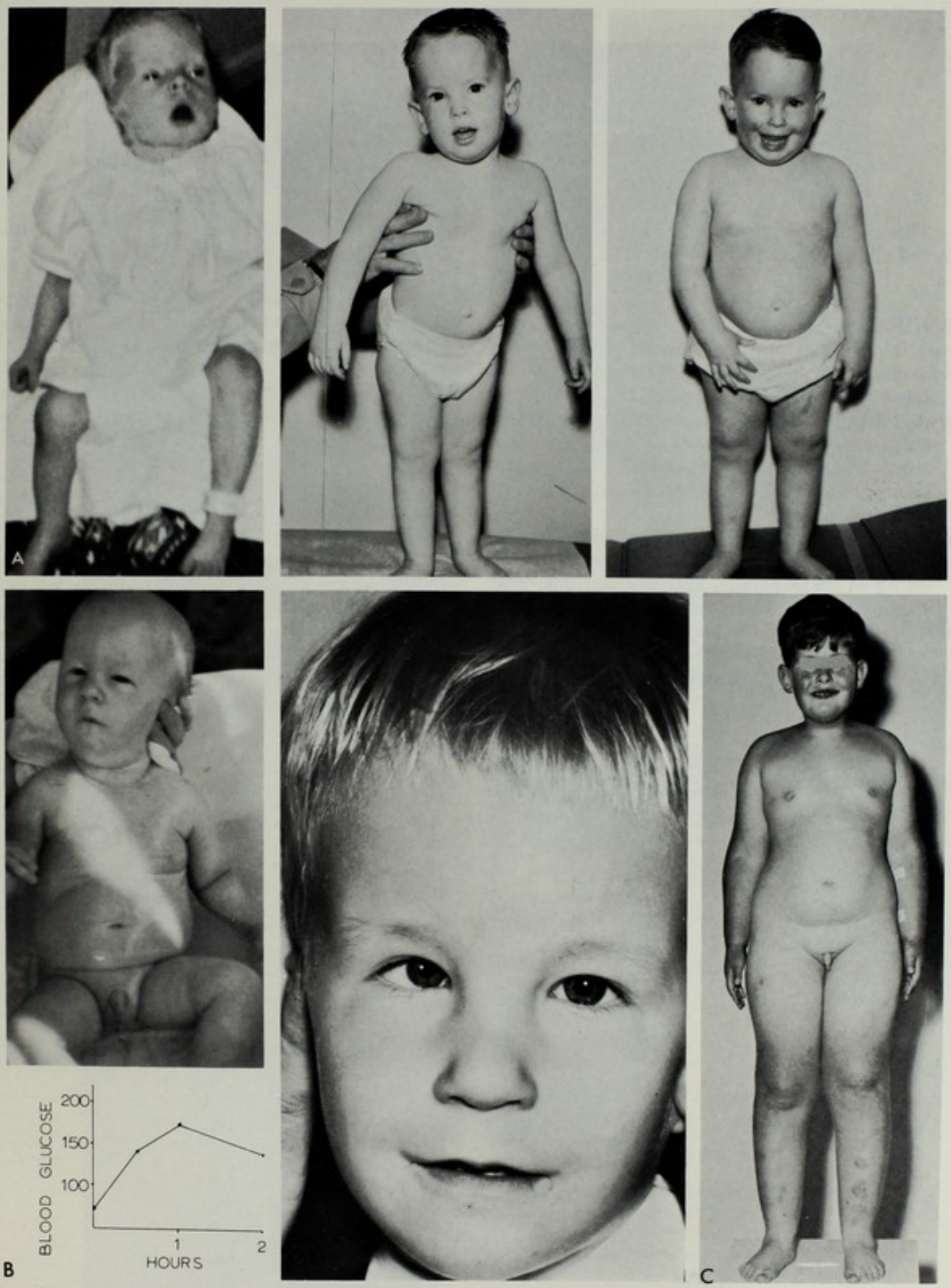
NATURAL HISTORY. The mother may have noted feeble fetal activity, and the baby is often born in the breech position. The hypotonia is most severe in early infancy when there may be respiratory and feeding problems, not uncommonly necessitating tube feeding. The degree of mental deficiency may appear to be greater in infancy than at a later age because of the severity of the hypotonia hindering developmental performance. Regarding behavior, these patients have been noted to be cheerful and good natured. However, behavioral problems, including stubbornness and rage-type responses, tend to become more frequent in later childhood. Birth weight tends to be low, and failure to thrive is frequent in early infancy with obesity presenting at one to three years of age, especially over the lower abdomen, buttocks, and thighs. The obesity paradoxically develops at a time when the hypotonia is improving. The caloric intake is less than usual for height (about 80 per cent). The caloric intake must be dropped to about 60 per cent of usual for height in order to control the progressive obesity. The presence of a diabetic-type of glucose tolerance curve relates to the severity of the obesity and only an occasional patient develops diabetes mellitus during childhood.

Early short-term testosterone therapy has resulted in enlargement of the micropenis to normal size for age. Any boy who is doing reasonably well at the age of adolescence should be considered for full testosterone replacement therapy, since his own production is usually inadequate.

ETIOLOGY. Unknown. Usually sporadic, with occasional instances of recurrence. Empiric recurrence risk about 1 to 3 per cent. Possibly the syndrome represents the consequence of a single localized defect in early hypothalamic and/or midbrain development.

REFERENCES

1. Prader, A., Labhart, A., and Willi, H.: Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand im Neugeborenenalter. Schweiz. Med. Wschr., *86*:1260, 1956.
2. Hall, B. D., and Smith, D. W.: Prader-Willi syndrome. J. Pediatr., *81*:286, 1972.
3. Hamilton, C. R., Scully, R. E., and Kliman, B.: Hypogonadotrophism in Prader-Willi syndrome. Am. J. Med., *52*:322, 1972.
4. Pipes, P. L., and Holm, V. A.: Weight control of children with Prader-Willi syndrome. J. Am. Diet. Assoc., *62*:520, 1973.



A, Same patient as neonate, at one and five sixths years, and at two and five sixths years (height age, two and one third years; developmental quotient, 60.)

B, Same patient at five months and at four and one sixth years, at which time height age was three and one sixth years, developmental quotient was 50, and response to an oral glucose load was abnormal.

C, Nine and one half year old with height age of seven and one half years and mental age of five years. (Courtesy of Prof. A. Prader, University Kinderspital, Zurich.)

COHEN SYNDROME

Hypotonia, Obesity, Prominent Incisors

This disorder was recognized in 1973 in two affected siblings and one isolated case by Cohen, et al.[1]

ABNORMALITIES. Based on three cases.

Growth. Obesity of midchildhood onset.

Performance. Persisting hypotonia and weakness. Mental deficiency; I.Q. 30 to 70.

Facies. High nasal bridge, maxillary hypoplasia with mild downslant to palpebral fissures, short philtrum, open mouth with prominent maxillary central incisors, and mild micrognathia.

Eye. Mottled retina, myopia, strabismus.

Limb. Narrow hands and feet with mild shortening of metacarpals and metatarsals, and simian creases. Hyperextensible joints.

Spine. Lumbar lordosis with mild scoliosis.

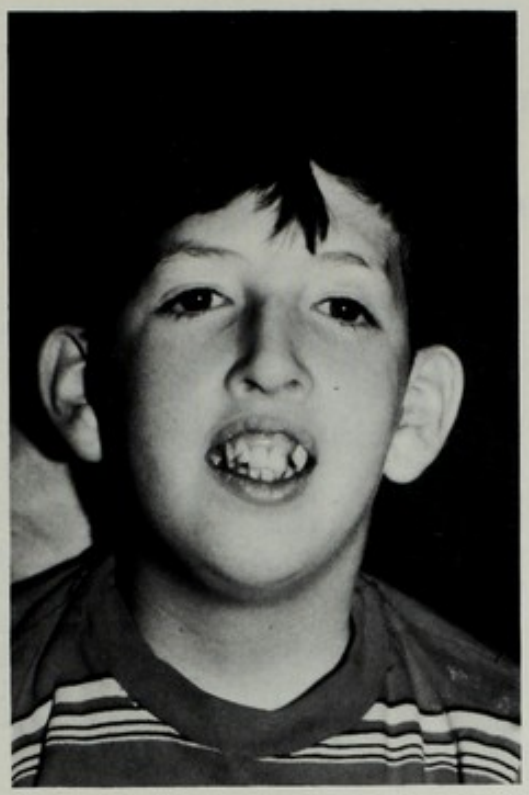
OCCASIONAL ABNORMALITIES. Found in one patient: microphthalmia, colobomata, mild cutaneous syndactyly.

NATURAL HISTORY. Weakness and hypotonia persist beyond infancy and obesity of moderate degree has developed in midchildhood.

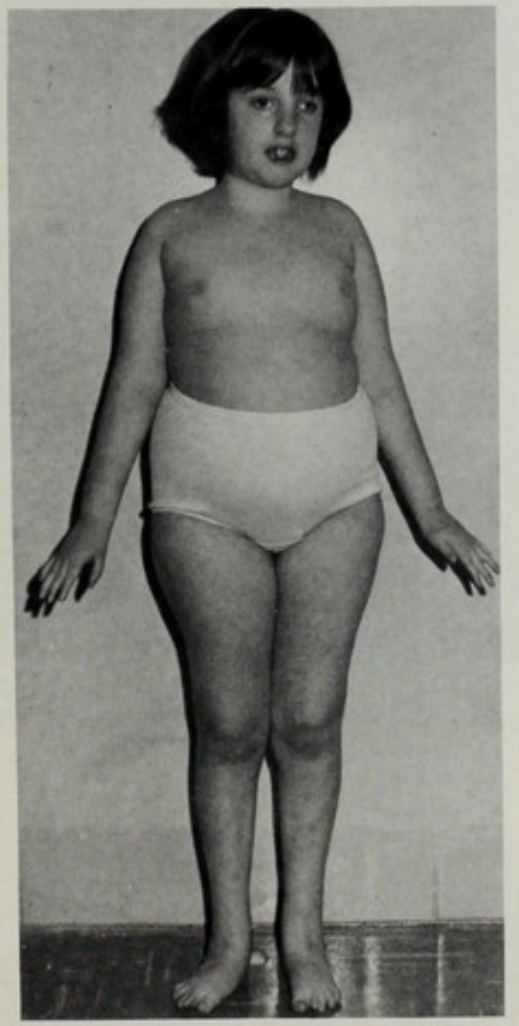
ETIOLOGY. Unknown. Occurrence in male and female siblings of normal parentage raises the potentiality of autosomal recessive inheritance.

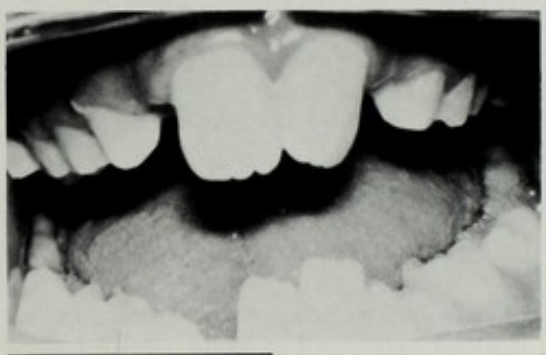
REFERENCES

1. Cohen, M. M., Jr., Hall, B. D., Smith, D. W., Graham, C. B., and Lampert, K. J.: A new syndrome with hypotonia, obesity, mental deficiency, and facial, oral, ocular, and limb anomalies. J. Pediatr., *83*:280, 1973.











Above, Brother and sister at 11 and 14 years of age, respectively.

Lower left, Eight year old who developed obesity at five to six years.

Lower right, Prominent central incisors and narrow hands with slim fingers.

(From Cohen, M. M., Jr.: J. Pediatr., *83*:280, 1973.)

ZELLWEGER SYNDROME

(Cerebro-Hepato-Renal Syndrome)

Hypotonia, High Forehead with Flat Facies, Hepatomegaly

Bowen, et al.[1] and Smith, et al.[2] independently reported siblings with this pattern of malformation in 1964 and 1965. More than 25 cases have been reported.

ABNORMALITIES

General. Growth deficiency; mean birth weight, 3300 g. Hypotonia, respiratory problems, poor suck. Variable seizures.

Brain. Macrogyria and polymicrogyria noted; also incomplete white matter and myelinization, gross defects of early brain development.

Craniofacial. Large fontanels. Flat occiput. High forehead with shallow supraorbital ridges and flat facies. Minor ear anomaly. Inner epicanthic folds, Brushfield's spots. Mild micrognathia. Redundant skin, neck.

Liver. Hepatomegaly with dysgenesis, including cirrhotic change.

Kidney. Albuminuria. Small cysts, chiefly of glomeruli.

Cardiac. Patent ductus arteriosus, septal defect.

Limbs. Variable contractures with camptodactyly, limited extension of knee, equinovarus deformity. Simian crease.

Other. Variable elevated serum iron and evidence of excess iron storage.

OCCASIONAL ABNORMALITIES. Cataract, glaucoma, nystagmus, cubitus valgus, ulnar deviation of hands, punctate mineralization in area of joint, deep sacral dimple, hypospadias, cryptorchidism, hypertrophied pylorus, single umbilical artery. Breech presentation.

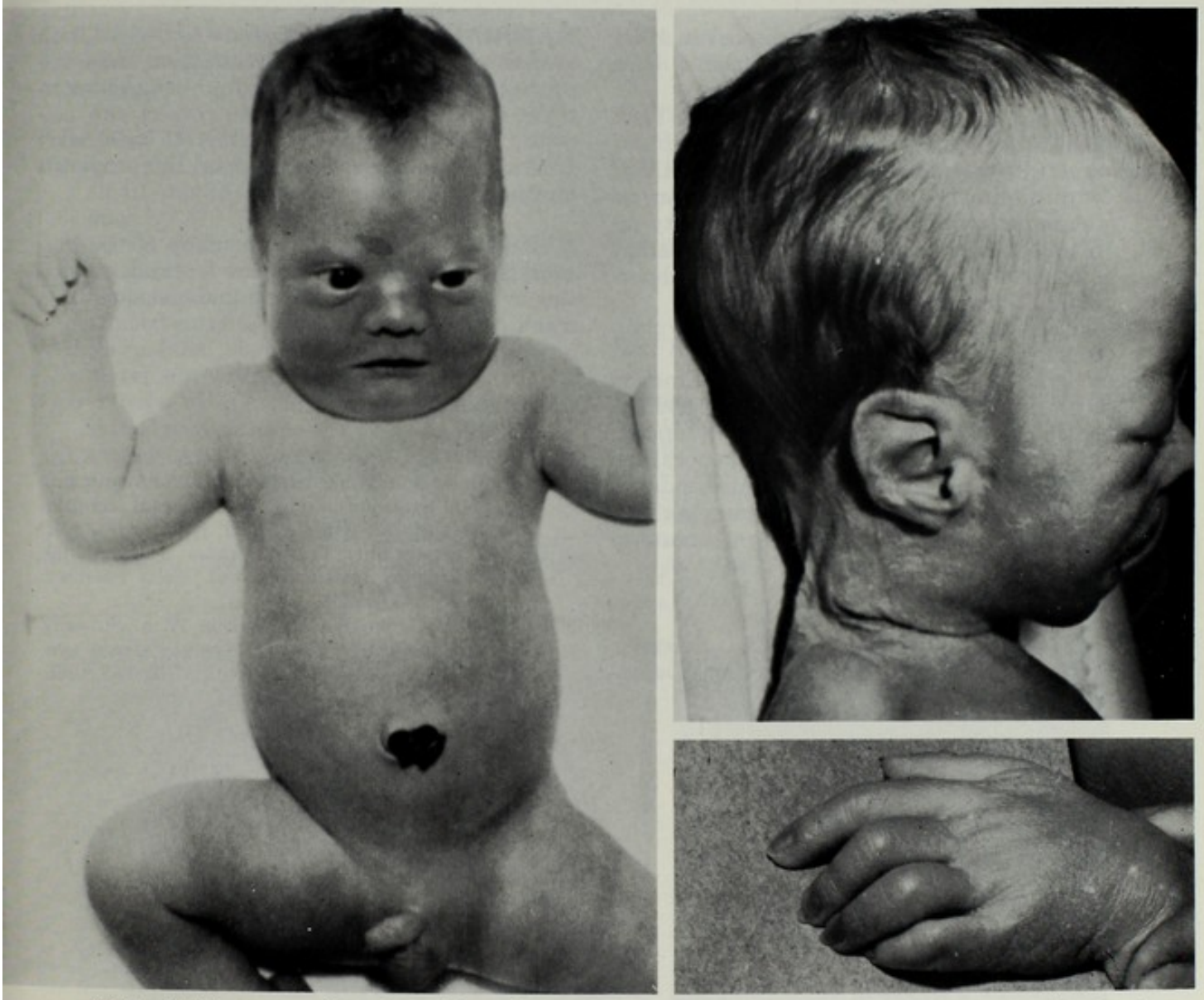
NATURAL HISTORY. Most of these babies were born in the breech presentation. They failed to thrive. Some develop icterus and some have bloody stools, possibly related to hypoprothrombinemia. All died from one day to six months after birth.

ETIOLOGY. Autosomal recessive. The reason for the tendency to have a high serum iron value and evidence of excess iron storage has not been clarified.

COMMENT. Several of these babies were mistakenly identified initially as having Down's syndrome. Chromosomal studies have been normal.

REFERENCES

1. Bowen, P., Lee, C. S. N., Zellweger, H., and Lindenberg, R.: A familial syndrome of multiple congenital defects. Bull. Hopkins Hosp., *114*:402, 1964.
2. Smith, D. W., Opitz, J. M., and Inhorn, S. L.: A syndrome of multiple developmental defects including polycystic kidneys and intrahepatic biliary dysgenesis in two siblings. J. Pediatr., *67*:617, 1965.
3. Opitz, J. M., et al.: The Zellweger syndrome, Birth Defects: Original Article Series, *5*:144, 1969.
4. Vincens, A., Guillat, J.-C., Gatin, G., Rodier, J., and Graveleau, D.: A propos d'un cas de syndrome de Zellweger (Syndrome Hépato-cérébro-rénal). Ann. Pediatr. (Paris), *20*:553, 1973.



Affected siblings at one day of age (left) and post mortem at ten weeks of age (right). Note camptodactyly of third, fourth, and fifth fingers. (From Smith, D. W., et al.: J. Pediatr., *67*:617, 1965.)

LOWE SYNDROME

(Oculo-Cerebro-Renal Syndrome)

Hypotonia, Cataract, Renal Tubular Dysfunction

Lowe, et al.[1] recognized this disease in 1952; subsequently more than 50 cases have been reported.

ABNORMALITIES

General. Hypotonia and joint hypermotility, with diminished to absent deep tendon reflexes and muscle hypoplasia with fatty infiltration. Hyperactivity. Mental deficiency, moderate to severe with diffuse EEG abnormality. Postnatal growth deficiency.

Eye. Cortical cataract with or without glaucoma.

Renal and Bone. Renal tubular dysfunction with limited ammonium production and hyperchloremic acidosis, phosphaturia tending toward hypophosphatemia, and generalized aminoaciduria. Albuminuria. Moderate to severe osteoporosis and sometimes rickets. There is also organic aciduria of unknown cause.

Gonad. Cryptorchidism.

OCCASIONAL ABNORMALITIES. Seizures. Pectus excavatum. Craniosynostosis. Dental cysts. Fracture.

NATURAL HISTORY. Failure to thrive. Both growth rate and bone mineralization may improve by administration of sodium-potassium citrate in adequate quantity to correct the acidosis. The prognosis for survival with such treatment is not known. However, the prognosis for brain function is poor.

ETIOLOGY. X-linked, with many of the heterozygote females showing fine lenticular opacities by slit lamp examination and occasionally a frank cataract.

REFERENCES

1. Lowe, C. U., Terrey, M., and MacLachland, E. A.: Organic-aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation. Am. J. Dis. Child.,*83*:164, 1952.
2. Illig, R., Dumermuth, G., and Prader, A.: Das oculocerebro-renale Syndrom (Lowe). Helv. Paediatr. Acta, *18*:173, 1963.
3. Richards, W., Donnell, G. N., Wilson, W. A., Stowens, D., and Perry, T.: The oculo-cerebro-renal syndrome of Lowe. Am. J. Dis. Child., *109*:185, 1965. 1965.

FREEMAN-SHELDON SYNDROME

(Whistling Face Syndrome)

Mask-Like "Whistling" Facies, Hypoplastic Alae Nasi, Club Feet

This disorder was described by Freeman and Sheldon[1] in 1938 and at least 28 cases have been reported.

ABNORMALITIES

Facies. Full forehead and mask-like facies with small mouth giving a "whistling" appearance.

Deep set eyes, broad nasal bridge, epicanthus, strabismus, blepharophimosis, small nose, hypoplastic alae nasi, long philtrum.

H-shaped cutaneous dimpling on chin.

High palate, small tongue, limited palatal movement with nasal speech.

Extremities. Ulnar deviation of hands, thick skin over flexor surface of proximal phalanges.

Equinovarus with contracted toes.

OCCASIONAL ABNORMALITIES. Blepharophimosis, ptosis, strabismus, subcutaneous ridge across lower forehead, small stature, low birth weight, scoliosis.

NATURAL HISTORY. Vomiting and swallowing difficulty may lead to failure to thrive in infancy. Eventual intelligence is said to be in the normal range.

ETIOLOGY. Autosomal dominant.

REFERENCES

1. Freeman, E. A., and Sheldon, J. H.: Cranio-carpo-tarsal dystrophy. An undescribed congenital malformation. Arch. Dis. Child., *13*:277, 1938.
2. Burian, F.: The "whistling face" characteristic in a compound cranio-facio-corporal syndrome. Br. J. Plast. Surg., *16*:140, 1963.
3. Walbaum, R., et al.: Le Syndrome de Freeman-Sheldon. Ann. Pediatr. (Paris), *49*:357, 1973.



A, Five and one half year old girl. Note crease pattern in chin.
B, Older boy. Note the retraction of the alae nasi.
(From Burian, F.: Br. J. Plast. Surg., *16*:140, 1963.)

STEINERT MYOTONIC DYSTROPHY SYNDROME

(Steinert Syndrome, Dystrophia Myotonica)

Myotonia with Muscle Atrophy, Cataract, Hypogonadism

The text by Caughey and Myrianthopoulos[1] presents the manifold abnormalities that may occur as features of this single mutant gene. Many hundreds of cases have been documented.

ABNORMALITIES[1-4]

Muscle Degeneration. Myotonia (difficulty in relaxing a contracted muscle), often best appreciated in the hand or jaw. Degeneration of swollen muscle cells giving way to thin and atrophic muscle fibers with weakness, ptosis of the eyelids is frequent.

Cataract. Cataract, often only evident as "myotonic dust" by slit lamp inspection.

Gonadal Insufficiency. Testicular atrophy (80 per cent) in males. Amenorrhea, dysmenorrhea, ovarian cyst in females.

Scalp. Premature frontal recession, especially in males.

Cardiac. Conduction defects with arrhythmias.

OCCASIONAL ABNORMALITIES. Hypotonia in infancy, mental deficiency, microcephaly, club foot, clinodactyly, hernia, cryptorchidism, kyphoscoliosis, hyperostotic cranial bones, atrophic thin skin, macular abnormality, blepharitis, keratitis sicca, goiter, thyroid adenomata, diabetes mellitus.

NATURAL HISTORY. The age of onset is from prenatal life to the sixth or seventh decade, with an average of the late 20's. Initial signs of the disease are variable. Myotonia may be so mild as to be detected only when specifically tested for. Muscle wasting and weakness, occasionally asymmetrical, most often involve the facial and temporal muscles, yielding the expressionless "myopathic facies." Other involved muscles are the anterior cervical and those of the arms, thighs, and anterior lower leg, with progression from proximal to distal. Ptosis of the eyelids is frequent and pseudohypertrophy is an occasional feature. One of the most sensitive early indications of muscle dysfunction is the roentgenographic evidence of partial retention of radiopaque material in the pharynx after swallowing. Mental deterioration may also be a feature. There is increasing debility with death, usually by the fifth or sixth decade, as a consequence of pneumonia, cardiac failure, or intercurrent illness.

Pruzanski[3] and Calderon[4] emphasize disease manifestations in pre-adolescent life and Bell and Smith note the potential prenatal manifestations. Some patients have been hypotonic and "floppy" with apparent mental defect during infancy.

ETIOLOGY. Autosomal dominant with wide variability in expression. Bundey and Carter provide evidence for genetic heterogeneity for this disorder, with at least two autosomal dominants: one in which the onset is usually in infancy and the other in which the onset is usually after 20 years of age.

REFERENCES

1. Caughey, J. E., and Myrianthopoulos, N. C.: Dystrophia Myotonica and Related Disorders. Springfield, Ill., Charles C Thomas, 1963.
2. Pruzanski, W.: Myotonic dystrophy—a multisystem disease; report of 67 cases and a review of the literature. Psychiatr. Neurol. Med. Psychol. (Leipz.), *149*:302, 1965.
3. Pruzanski, W.: Variants of myotonic dystrophy in pre-adolescent life (the syndrome of myotonic dysembryoplasia). Brain, *89*:563, 1966.
4. Calderon, R.: Myotonic dystrophy: a neglected cause of mental retardation. J. Pediatr., *68*:423, 1966.
5. Bell, D. B., and Smith, D. W.: Myotonic dystrophy in the neonate. J. Pediatr., *81*:83, 1972.
6. Bundey, S., and Carter, C. L.: Genetic heterogeneity for dystrophia myotonica. J. Med. Genet., *9*:311, 1972.





Above, Severely affected almost immobile newborn baby of mother with myotonic dystrophy. (From Bell, D. B., and Smith, D. W.: J. Pediatr., *81*:83, 1972.)

Right, Fourteen year old with relatively immobile facies, scoliosis, I.Q. of 58.

Below, Correlation of protean features of myotonic dystrophy with age of onset, beginning with earliest age reported.

	FETAL–NEONATAL INFANCY	CHILDHOOD	ADULTHOOD
CNS	Mental deficiency ———		
OCULAR	Cataracts ———		
	Ptosis ———		
SKELETAL	Clubfeet		
		Scoliosis / lordosis ———	
		Cranial hyperostosis ———	
RESPIRATORY	Neonatal distress		
	Recurrent infection ———		
			Chronic insufficiency
NEURO-MUSCULAR	Hypotonia / "floppy"		
	Facial diplegia		
	Weakness / atrophy ———		
	Variable myotonia ———		
		Dysarthria ———	
GI	Poor feeding		
	Impaired deglutition ———		
GONADAL	Cryptorchidism ———		
			Hypogonadism
CARDIAC		Disturbed conduction ———	
MISC.		Frontal baldness ———	
		Decreased IgG and IgM ———	

SCHWARTZ SYNDROME

Myotonia, Blepharophimosis, Joint Limitation

Though Pinto and de Sousa were the first to report this disorder, this fact was only recently appreciated. Schwartz and Jampel described a brother and sister with this condition in 1962, and later Aberfeld et al. reported further observations on the same patients. At least seven cases have been reported.

ABNORMALITIES

Growth. Small stature, usually postnatal onset.

Muscle. Myotonia with sad, fixed facies.
Hypoplasia with atrophy and small muscle fibers.

Joint. Limitation in hips, wrist, fingers, toes, and spine.
Equinovarus (one patient).

Osseous. Vertical shortness of vertebrae with short neck.
Fragmentation and flattening of femoral epiphyses.
Pectus carinatum.

Larynx. Small with high pitched voice.

Eye. Blepharophimosis, myopia.
Long eyelashes in irregular rows. Flat facies.

Other. Low hairline, low set ears, small testicles.

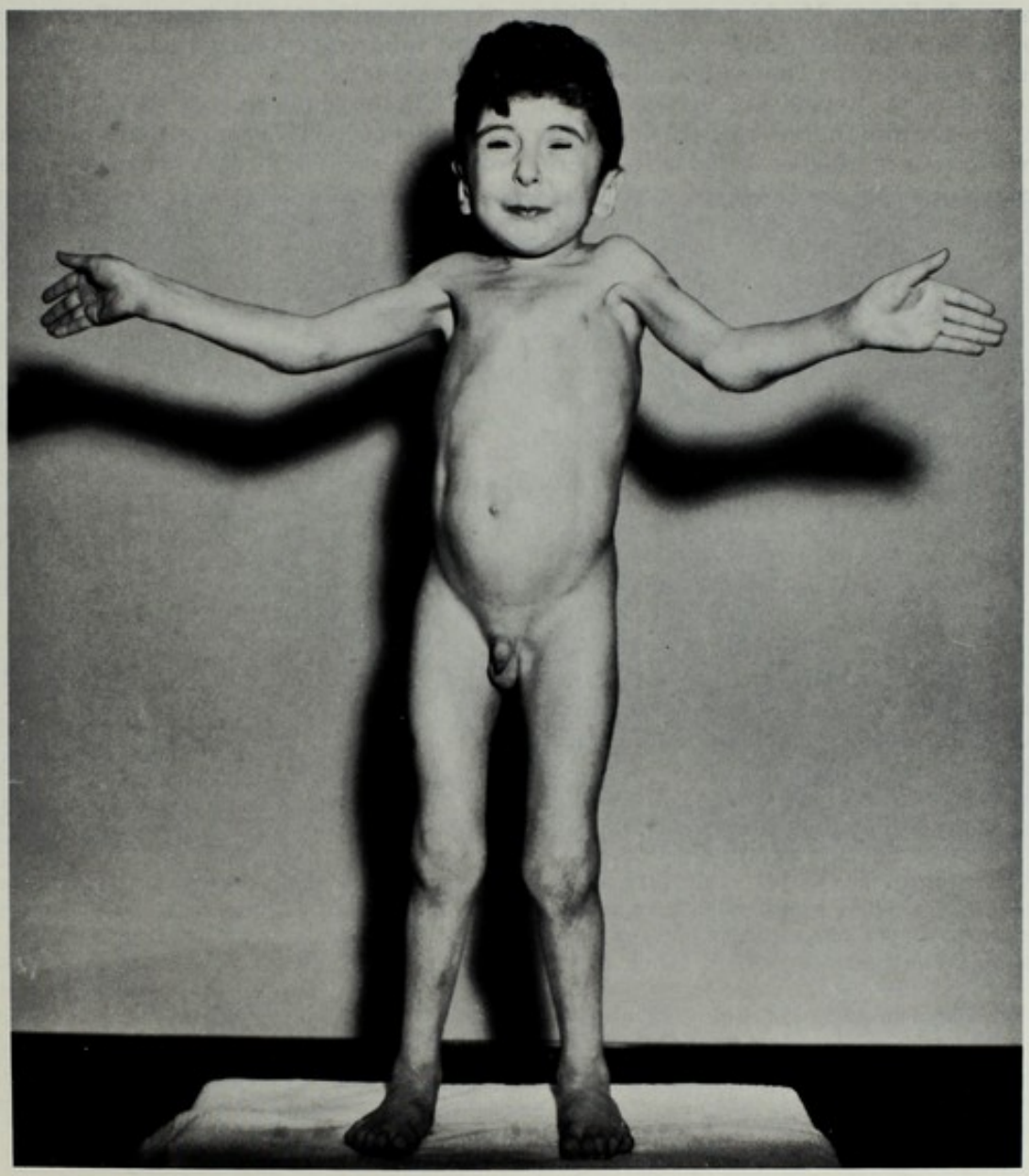
NATURAL HISTORY. Onset of progressive myotonia, muscle wasting, and orthopedic problems during infancy with slow linear growth.

ETIOLOGY. Autosomal recessive considered the most likely mode of etiology.

COMMENT. This disease appears to be a specific disorder of connective tissue in which deterioration occurs during infancy and childhood.

REFERENCES

1. Pinto, L. M., and de Sousa, J. S.: Um caso de "doenca muscular" de dificil classificacao. Rev. Port. Pediatr. Pueric., *6*:1, 1961.
2. Schwartz, O., and Jampel, R. S.: Congenital blepharophimosis associated with a unique generalized myopathy. Arch. Ophthalmol., *68*:52, 1962.
3. Aberfeld, D. C., Hinterbuchner, L. P., and Schneider, M.: Myotonia, dwarfism, diffuse bone disease and unusual ocular and facial abnormalities (a new syndrome). Brain, *88*:313, 1965.
4. Santesteban, A.: Schwartz syndrome. J. Pediatr., *82*:1094, 1973.



Six year old male with height age of three and one half years. A female sibling had the same disorder and the parents appeared normal. (From Schwartz, O., and Jampel, R. S.: Arch, Ophthalmol, *68*:52, 1962.)

MOEBIUS ANOMALAD

Primary Defect—In Cranial Nerve Nuclei

The basic finding in Moebius anomalad is a mask-like facies with sixth and seventh nerve palsy, usually bilateral. The few well-studied necropsy cases show hypoplasia to agenesis of the respective cranial nerve nuclei. Clinically the patients have a mask-like facies with lateral rectus ocular palsy (75 per cent). Micrognathia, a frequent feature, may be interpreted as secondary to a neurologic deficit in early movement of the mandible. Some patients have more extensive cranial nerve involvement, including third, fourth, ninth, tenth, twelfth, and hypoglossal nerves. In the latter cases the tongue may be limited in mobility and/or small. There may be ocular ptosis. About a third of the patients have talipes equinovarus, which might be the consequence of neurologic deficiency relative to early foot movement; about 15 per cent have mental deficiency as a more obvious indication that the CNS defect involves more than the cranial nerve nuclei alone.

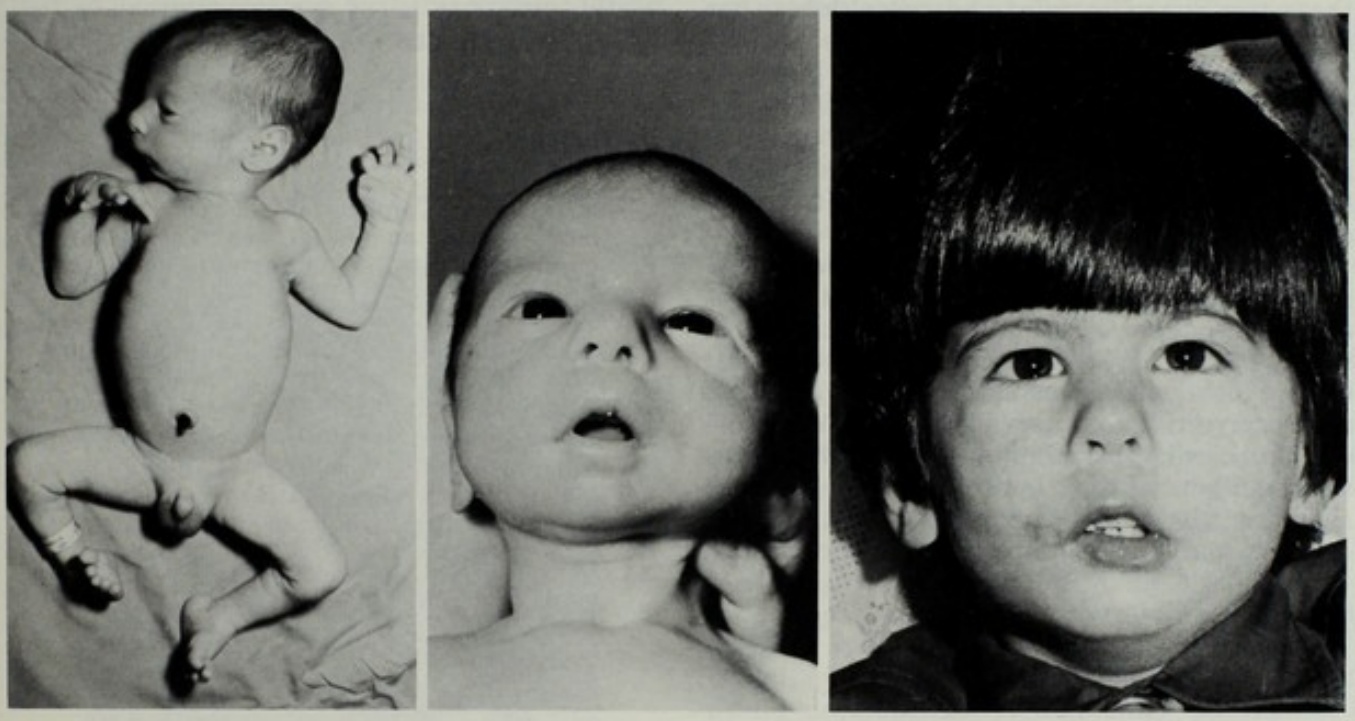
Feeding difficulties and problems of aspiration often lead to failure to thrive during infancy. The expressionless facies and speech problems create problems in acceptance and social adaptation.

The Moebius anomalad is most commonly a sporadic occurrence in an otherwise normal family, although rare instances of autosomal dominant inheritance with variable expression have been reported.

The Moebius anomalad may be a part of a broader pattern of malformation. Associated occasional non-CNS related defects have included limb reduction defects, syndactyly, and absence of pectoralis major muscle. One interesting case had features of both the Moebius anomalad and the Poland anomalad.

REFERENCES

1. Moebius, P. J.: Ueber engeborene doppelseitige Abducens-Facialis-Laehmung. Munch. Med. Wochenschr., *35*:91, 1888.
2. Henderson, J. L.: The congenital facial diplegia syndrome. Clinical features, pathology, and aetiology. A review of sixty-one cases. Brain, *62*:381, 1939.
3. Richards, R. N.: The Möbius syndrome. J. Bone Joint Surg. [Am.], *35*:437, 1953.
4. Reed, H., and Grant, W.: Möbius syndrome. Br. J. Ophthalmol., *41*:731, 1957.
5. Van der Wiel, H. J.: Hereditary facial paralysis. Acta Genet. Statist. Med., *7*:348, 1957.
6. Sugarman, G. I., and Stark, H. H.: Möbius anomaly with Poland's anomaly. J. Med. Genet., *10*:192, 1973.



Left and *Middle,* Newborn with Moebius anomalad showing high nasal bridge, micrognathia with limited mandibular movement, small mouth with downturned corners, expressionless facies with deficit of lateral gaze, mild ptosis, mild talipes, and mild alteration in finger positioning. These clinical findings were interpreted as being the secondary neurologic consequence of a single primary defect in CNS development, especially of the nuclei of the sixth and seventh nerves.

Right, Same patient at three years of age. He had achieved limited ability to open his mouth, was responding well to speech training, and was interpreted as having normal intelligence.

ASYMMETRIC CRYING FACIES–CARDIAC DEFECT ASSOCIATION

Cayler[1] noted asymmetric crying facies in a total of 14 children being evaluated because of a cardiac defect. Chantler and McEnery[2] searched for asymmetric crying facies in hospitalized children and found 44 patients, among whom 50 per cent had a cardiac defect as well. The most common type of cardiac anomaly was ventricular septal defect. The majority of the patients with these two anomalies also had other defects, including vertebral anomalies, anal atresia, radial hypoplasia, and renal defects. As may be noted, these are anomalies found in the VATER association. Hence the question is raised as to whether asymmetric crying facies might not be a frequent feature in the broader VATER association, which includes cardiac anomaly.

Studies have implied that asymmetric crying facies is most commonly due to partial agenesis of the depressor anguli oris muscle rather than a facial palsy.[3] The finding of this anomaly in an otherwise normal-appearing newborn should give rise to a cautious clinical examination for cardiac or other anomalies. Providing the remainder of the examination is negative, it should not lead to undue concern. Perlman and Reisner[4] found asymmetrical crying facies in 44 (0.6 per cent) of a series of 6,360 newborn babies, of whom two (4.9 per cent) had a major defect, one having a cardiac anomaly.

Of potential interest was the observation that the facial asymmetry was 83 per cent left-sided in the normal series of babies, but 68 per cent right-sided in those with cardiac and/or other defects. Thus right-sided facial asymmetry would appear to be of more concern than left-sided involvement.

REFERENCES

1. Cayler, C. G.: Cardiofacial syndrome. Congenital heart disease and facial weakness, a hitherto unrecognized association. Arch. Dis. Child., *44*:69, 1969.
2. Pape, K. E., Pickering, D.: Asymmetric crying facies: An index of other congenital anomalies. J. Pediatr., *81*:21, 1972.
3. McHugh, H. E., Sowden, K. A., and Levitt, M. N.: Facial paralysis and muscle agenesis in the newborn. Arch. Otolaryngol., *89*:131, 1969.
4. Perlman, M., and Reisner, S. H.: Asymmetric crying facies and congenital anomalies. Arch. Dis. Child., *48*:627, 1973.

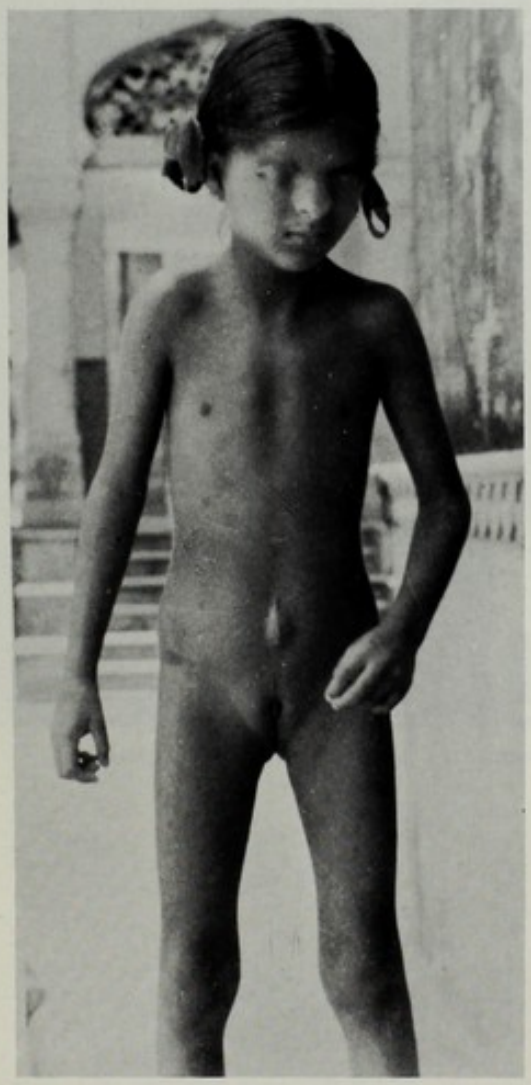
CRYPTOPHTHALMOS SYNDROME

(Fraser Syndrome)

Cryptophthalmos, Defect of Auricle, Genital Anomaly*

The association of multiple other malformations in patients with the rare anomaly of cryptophthalmos had been appreciated prior to 1962, when a rather distinctive syndrome found in two sets of siblings was set forth by Fraser.[1] About 50 cases have been reported. The syndrome needs further definition and the following represents a preliminary depiction of this condition.

*Cryptophthalmos (hidden eye) fundamentally means absence of the palpebral fissure but usually includes varying absence of eyelashes and eyebrows and defects of the eye, especially the anterior part.



A genetic male with cryptophthalmos, malformed ears with atresia of external auditory canals, aberrant umbilicus, and incomplete development of external genitalia. (Courtesy of S. P. Gupta, University of Lucknow.)

PATTERN OF ABNORMALITY. The most consistent features have been the following:

Facial. Cryptophthalmos, usually with defect of eye. Hair growth on lateral forehead extending to lateral eyebrow. Hypoplastic notched nares. Ear anomaly, most commonly cupped.

Limbs. Partial cutaneous syndactyly.

Genitalia. Incomplete development. Male—hypospadias, cryptorchidism. Female—bicornuate uterus, vaginal atresia.

OCCASIONAL FEATURES. Flat nasal bridge, hypertelorism, lacrimal duct defect, palatal defect, partial mid-facial cleft, atresia of external ear canal, defect of middle ear, laryngeal stenosis or atresia, widely spaced nipples, renal anomaly, umbilical anomaly, anal atresia.

NATURAL HISTORY. Two of the four patients reported by Fraser[1] were stillborn. As yet no clear statement as to survival or mental retardation can be set forth. Because the defect of eyelid development is frequently accompanied by ocular anomaly, the likelihood of achieving adequate visual perception is small, although early surgical intervention was of value in one case.

ETIOLOGY. Autosomal recessive implied for the syndrome. There may be etiologic heterogeneity for the cryptophthalmos anomaly.

REFERENCES

1. Fraser, C. R.: Our genetical "load." A review of some aspects of genetical variation. Ann. Hum. Genet., *25*:387, 1962.
2. Gupta, S. P., and Saxena, R. C.: Cryptophthalmos. Brit. J. Ophthalmol., *46*:629, 1962.
3. François, J.: Syndrome malformatif avec cryptophthalmie. (Note préliminaire.) Ophthalmologica, *150*:215, 1965.
4. Schonenberg, H.: Kryptophthalmos-syndrom. Klin. Paediatr., *185*:165, 1973.
5. Azvedo, E. S., Biondi, J., and Ramaldo, L. M.: Cryptophthalmos in two families. J. Med. Genet., *10*:389, 1973.

BLEPHAROPHIMOSIS SYNDROME

(Familial Blepharophimosis Syndrome)

Inner Canthal Fold, Lateral Displacement of Inner Canthi, Ptosis

This entity, predominantly a dysplasia of the eyelids, was described by Vignes[1] in 1889 and more than 125 cases have been reported.

ABNORMALITIES

Eyes. Inverted inner canthal fold between upper and lower lid, short palpebral fissures with lateral displacement of inner canthi, low nasal bridge and ptosis of eyelids, with hypoplasia and fibrosis of the levator palpebrae muscle.

OTHER ABNORMALITIES. Possible general hypotonia, strabismus, nystagmus. Prominent cupped auricles.

NATURAL HISTORY. Plastic surgery is indicated both for cosmetic reasons and for improvement of ocular function.

ETIOLOGY. Autosomal dominant.

COMMENT. The facial appearance may initially suggest a condition with associated mental retardation; however, the affected individuals are not generally mentally deficient. Sacrez et al.[2] reported I.Q.'s from 75 to 100, with a mean value of 86.

REFERENCES

1. Vignes: Epicanthus héréditaire. Rev. Gen. Ophtalmol. (Paris), *8*:438, 1889.
2. Sacrez, R., Francfort, J., Juif, J. G., and de Grouchy, J.: Le blépharophimosis compliqué familial. Étude des membres de la famille Ble. Ann. Pediatr. (Paris), *10*:493, 1963.
3. Kohn, R., and Romano, P. E.: Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus—a syndrome with no name. Am. J. Ophthalmol., *72*:625, 1972.



Mother and infant daughter, with insert of the mother as a child, prior to surgical repair.

WAARDENBURG SYNDROME

Lateral Displacement of Medial Canthi, Partial Albinism, Deafness

Waardenburg[1] set forth this pattern of malformation in 1951. He found this syndrome in 1.4 per cent of congenitally deaf children and from these data estimated the incidence to be about 1:42,000 in Holland.

ABNORMALITIES

Lateral displacement of inner canthi	99%
Broad and high nasal bridge	78%
Medial flare of eyebrows, which may meet in midline	45%
Partial albinism	37%
Deafness	20%

OCCASIONAL ABNORMALITIES. Hypoplasia of alae nasi, rounded tip of nose, full lips with accentuated "cupid's bow" to upper lip, cleft lip and palate, cardiac anomaly (VSD), limb defect.

NATURAL HISTORY. The partial albinism is most commonly expressed as a white forelock and/or isochromic beautiful pale blue eyes with hypoplastic iral stroma; however, it may be present as heterochromia of the iris, areas of viteligo on the skin, patches of white hair other than the forelock, and/or mottled peripheral pigmentation of the retina. The white forelock may be present at birth only to become pigmented early in life; the hair may become prematurely gray or white.

Congenital deafness is the most serious feature and if present is usually bilateral and severe. The defect appears to be in the organ of Corti with atrophic changes in the spiral ganglion and nerve.

ETIOLOGY. Autosomal dominant. Five of the 16 propositi of Waardenburg were considered to represent fresh mutations, a calculated mutation rate of 0.4×10^{-5} per gamete. Older paternal age has been a factor in the fresh mutation cases.

COMMENT. The association of dominantly inherited albinism and deafness was noted in cats as early as 1769 and subsequently in the horse and several types of dog.

REFERENCES

1. Waardenburg, P. J.: A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. Am. J. Hum. Genet., *3*:195, 1951.
2. DiGeorge, A. M., Olmsted, R. W., and Harley, R. D.: Waardenburg's syndrome. J. Pediatr., *57*:649, 1960.
3. Pryor, H. B.: A case of Waardenburg's syndrome. Am. J. Dis. Child., *122*:177, 1971.



A, Mother and daughter. Note the isochromic light iris. (From Partington, M. W.: Arch. Dis. Child., *34*:154, 1959.)

B, Ten year old with congenital deafness. Note prominent nasal root, small alae nasi. (From DiGeorge, A. M., et al.: J. Pediatr., *57*:649, 1960.)

C, Brothers, only one of whom has deafness. Note the lack of a white forelock.

D, Four month old infant who had a white forelock at birth which is now pigmented. Note heterochromia of irises, lateral placement of inner canthi, and small alae nasi.

OPITZ SYNDROME

(Hypertelorism-Hypospadias Syndrome)

Hypertelorism, Hypospadias

Opitz, Summitt, and Smith[1,2] reported this dominantly inherited condition in three families in which affected males usually have apparent ocular hypertelorism and hypospadias, whereas affected females have only hypertelorism, there being no opportunity for expression of the penile malformation in the female.

ABNORMALITIES
Facial. Ocular hypertelorism. Widow's peak.
Genital. Hypospadias, cryptorchidism.
Other. Herniae.

OCCASIONAL ABNORMALITIES. Mental deficiency, cardiac anomaly, posterior rotation anomaly of auricle, cleft lip plus or minus palate.

ETIOLOGY. ? Autosomal dominant with sex limitation for penile malformation. One probable instance of male-to-male transmission tentatively excludes X-linked inheritance.

REFERENCES

1. Opitz, J. M., Smith, D. W., and Summitt, R. L.: Hypertelorism and hypospadias. (Abstract.) J. Pediatr., *67*:968, 1965.
2. Opitz, J. M., Summitt, R. L., and Smith, D. W.: The BBB Syndrome. Familial Telecanthus with Associated Anomalies. First Conference on Clinical Delineation of Birth Defects. D. Bergsma, Editor. Vol. 5, 86–94, 1969, The National Foundation.
3. Michaelis, E., and Mortier, W.: Association of hypertelorism and hypospadius. Helv. Paediatr. Acta, *27*:575, 1972.



An affected mother (mild hypertelorism) and two of her affected boys who show hypertelorism and also have hypospadias. (From the B. O. family pedigree of Opitz, et al.: Birth Defects, *5*:86, 1969.)

FRONTONASAL DYSPLASIA ANOMALAD

(Median Cleft Face Syndrome)

Unknown Primary Defect in Midfacial Development with Incomplete Anterior Appositional Alignment of Eyes

DeMyer[1] recognized the transitional gradations in severity of this presumed single primary localized defect in 33 cases and termed the pattern of anomaly the median facial cleft syndrome. Sedano, et al.[2] subsequently extended these observations and recommended frontonasal dysplasia as a more appropriate designation for this defect. The accompanying figure sets forth a crude interpretation of the developmental pathogenesis and gradations of the anomalad.

ABNORMALITIES. Defects which may occur in the more severe cases; the milder cases may have only a few of the defects.

Eye. Ocular hypertelorism. Lateral displacement of inner canthi.

Forehead. Widow's peak. Deficit in midline frontal bone (cranium bifidum occultum).

Nose. Variability from notched broad nasal tip, to completely divided nostrils with hypoplasia, to absence of the prolabia and premaxilla with a median cleft lip. Variable notching of ala nasae.

Mouth. Median cleft palate, double frenulum.

OCCASIONAL ABNORMALITIES. Accessory nasal tags. Midline lipoma, dermoid. Microphthalmia. Preauricular tags, low-set ears, conductive deafness. Coronal craniosynostosis. Absence of corpus callosum. Mental deficiency.

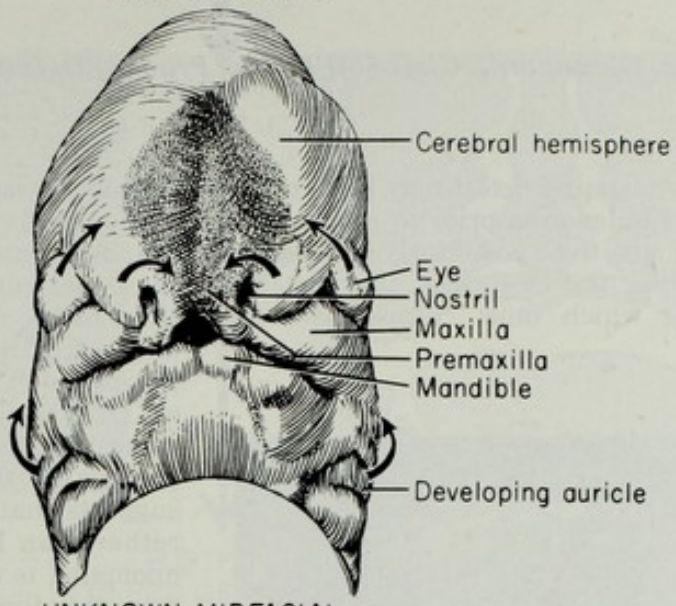
NATURAL HISTORY. Depending on the severity of the defect, radical cosmetic surgery is usually merited. The majority of affected individuals are of normal intelligence. DeMyer noted 8 per cent severe mental deficiency and 12 per cent mild impairment of intelligence.

ETIOLOGY. Unknown. Generally a sporadic occurrence. An occasional relative may have a mild degree of the anomalad.

REFERENCES

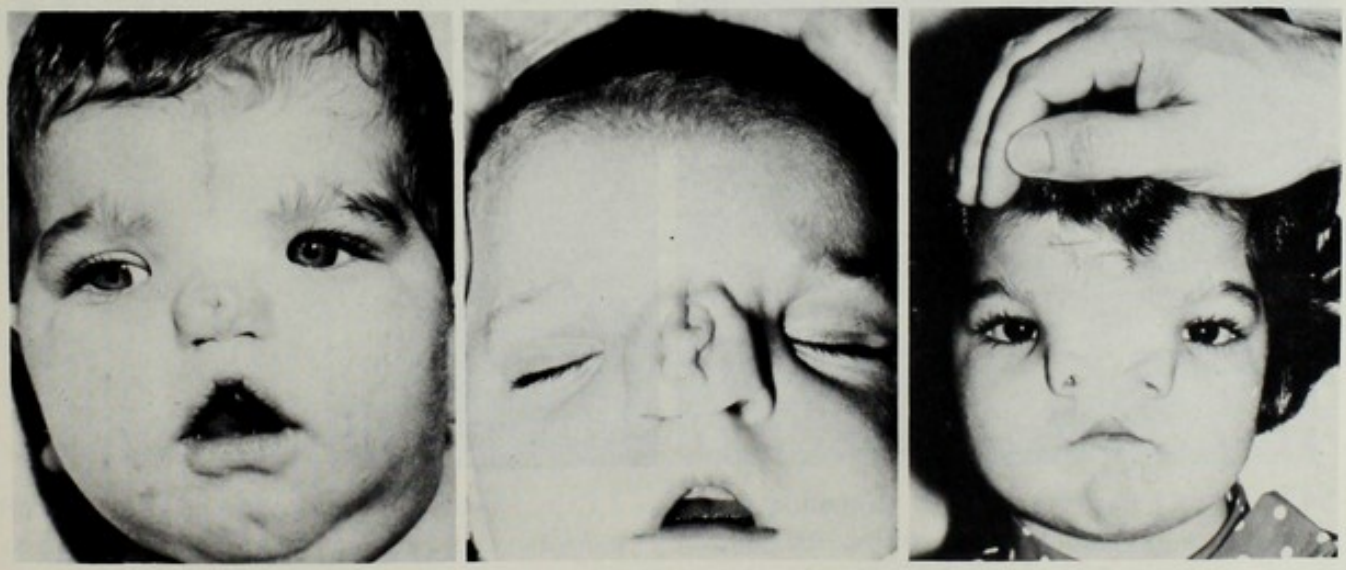
1. DeMyer, W.: The median cleft face syndrome. Differential diagnosis of cranium bifidum occultum, hypertelorism, and median cleft nose, lip, and palate. Neurology [Minneap.], *17*:961, 1967.
2. Sedano, H. O., Cohen, M. M., Jr., Jirasek, J., and Gorlin, R. J.: Frontonasal dysplasia. J. Pediatr., *76*:906, 1970.

FRONTONASAL DYSPLASIA
ANOMALAD



UNKNOWN MIDFACIAL PRIMARY DEFECT

- Variable bifid nose
  - Broad notched nasal tip to bifid nostrils
  - Median cleft lip
- Failure of apposition of eyes
  - Broad nasal bridge
    - Telecanthus
  - Ocular Hypertelorism
    - Widow's peak
- Midline deficit of frontal bone

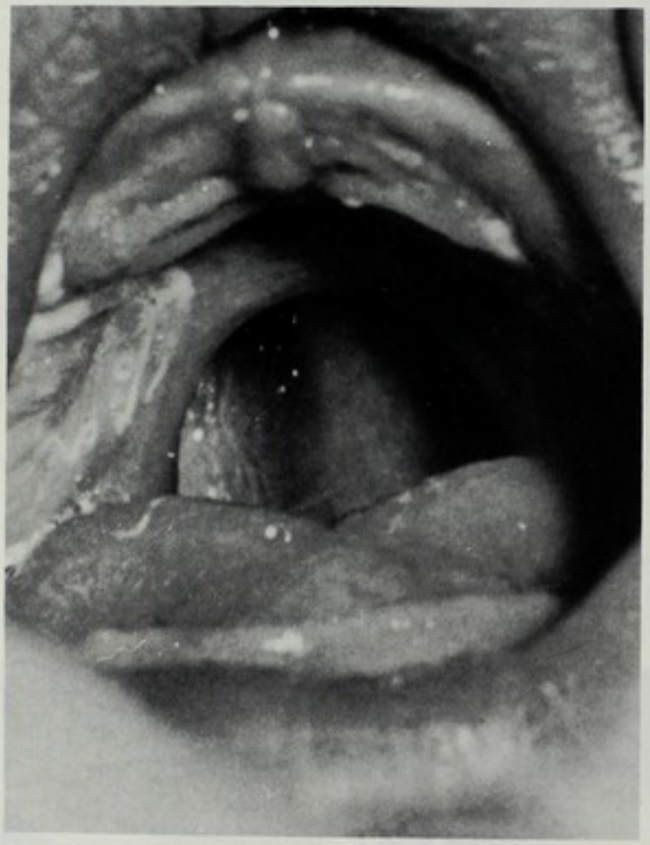


ROBIN ANOMALAD

(Pierre Robin Syndrome)

Micrognathia, Glossoptosis, Cleft Soft Palate; Primary Defect—Early Mandibular Hypoplasia

The single initiating defect may be hypoplasia of the mandibular area prior to nine weeks, allowing the tongue to be posteriorly located and thereby impairing the closure of the posterior palatal shelves which must "grow over" the tongue to meet in the midline. The mode of pathogenesis is depicted to the right. The rounded contour of the "cleft" palate in some of these patients (see below) is compatible with this mode of developmental pathology, and differs from the usual inverted V shape of most palatal clefts. Latham's study of a 17 week old fetus with the Robin anomalad led him to the same conclusion: that early mandibular retrognathia is the primary anomaly. The author suggests that this be termed "Robin anomalad" rather than Pierre Robin syndrome. The Robin anomalad is most commonly noted in otherwise normal individuals, whose prognosis is very good if they survive the early period of respiratory obstruction. Less commonly the anomalad may be one feature in a multiple defect syndrome such as the trisomy 18 syndrome. It is potentially quite misleading if all patients with the Robin anomalad are linked together under the Robin syndrome, thus including those individuals with multiple primary defects of diverse etiology and prognosis.



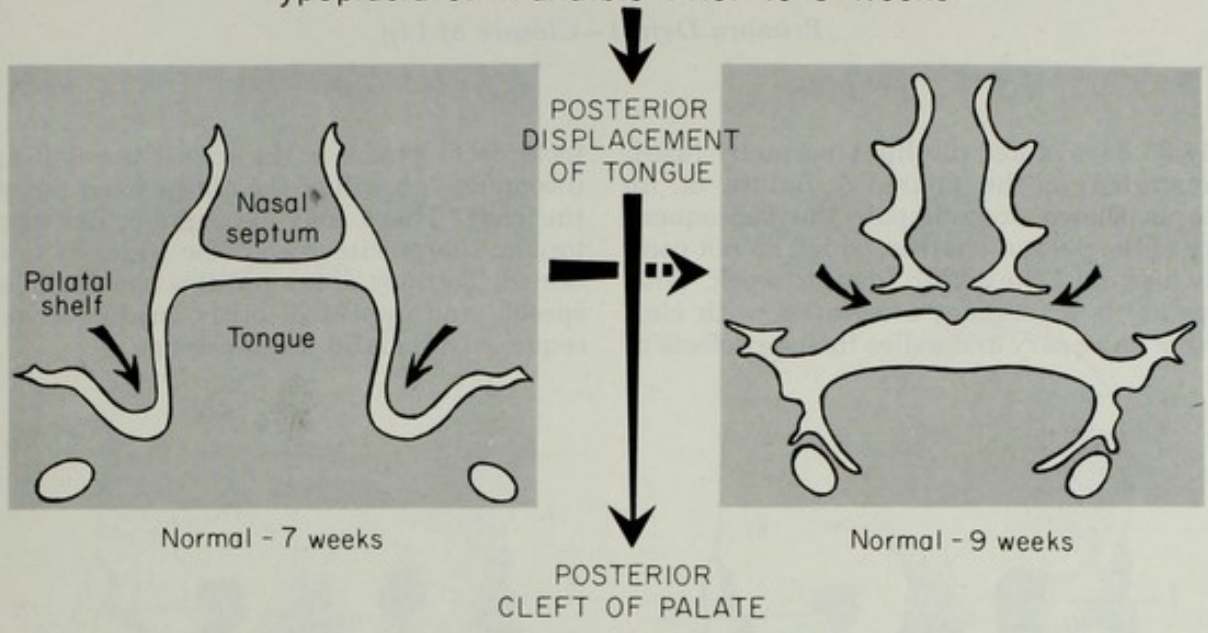
Unusual rounded shape to palatal "cleft" in a patient with the Robin anomalad, compatible with the incomplete closure of the palate having been secondary to the posterior displacement of the tongue.

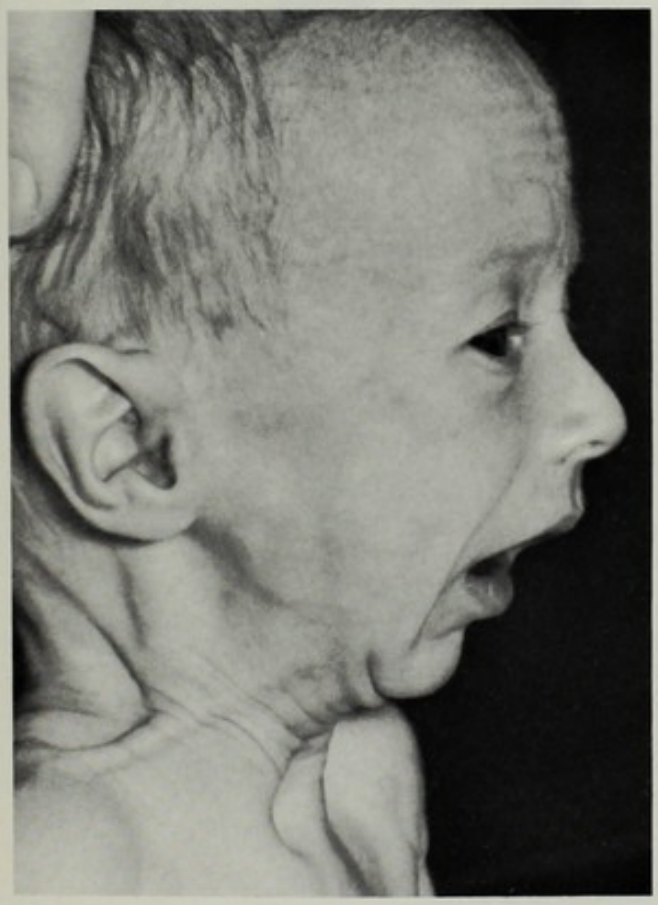
REFERENCES

1. Dennison, W. M.: The Pierre Robin syndrome. Pediatrics, *36*:336, 1965.
2. Latham, R. A.: The pathogenesis of cleft palate associated with the Pierre Robin syndrome. Br. J. Plast. Surg., *19*:205, 1966.

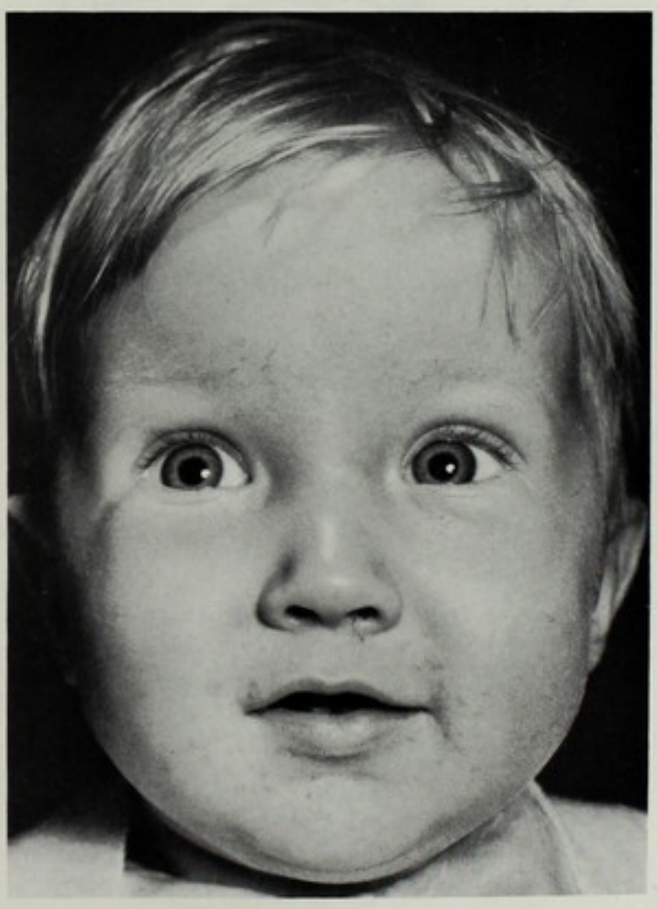
ROBIN ANOMALAD

A Primary Anomaly in Mandibular Development
Hypoplasia of Mandible Prior to 9 Weeks





Robin anomalad with upper respiratory obstruction and failure to thrive in 3 week old (weight, 4.9 lbs.)

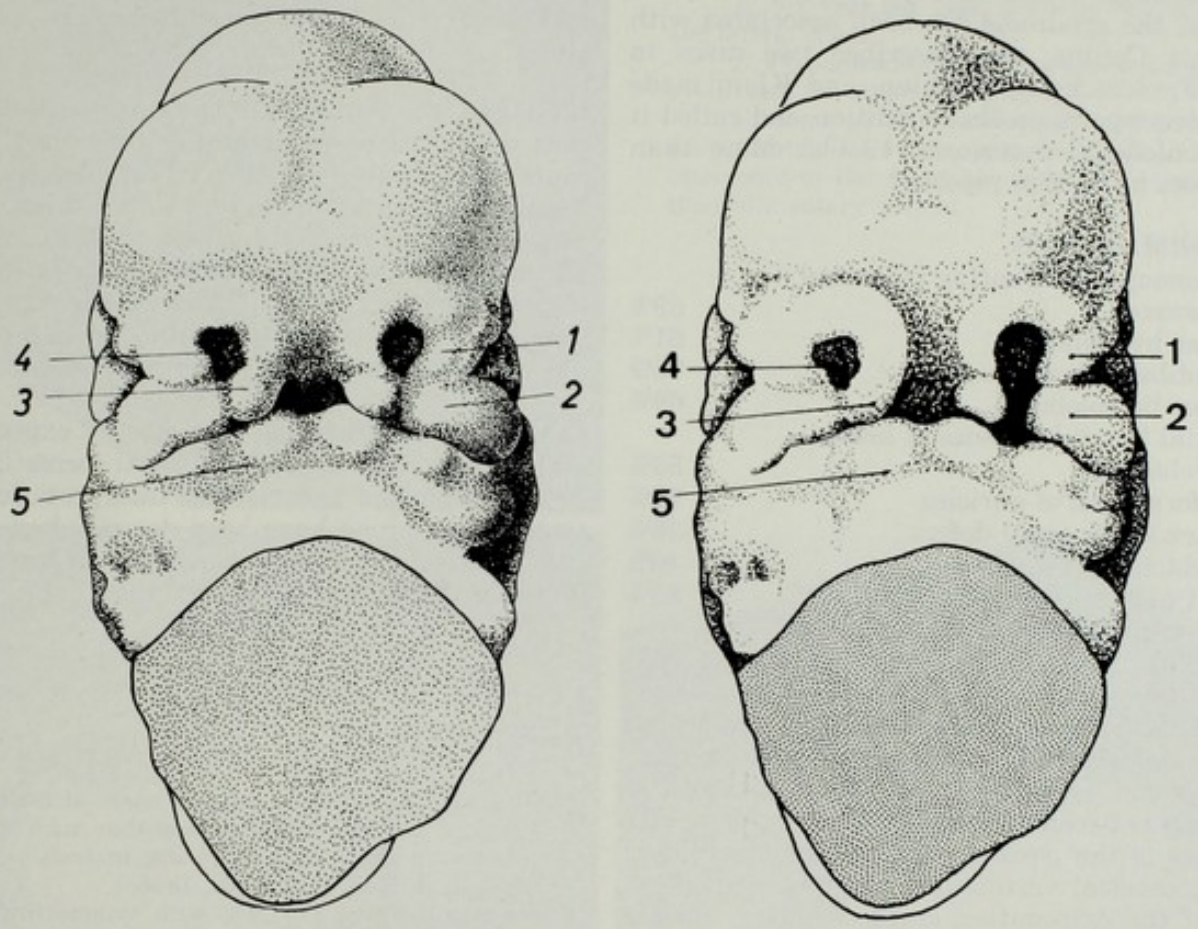


Same patient at 13 months showing catch-up in mandibular growth. Patient thriving with normal growth (weight, 14.8 lbs.).

CLEFT LIP AND PALATE ANOMALAD

Primary Defect—Closure of Lip

By 35 days of age the lip is normally fused, as illustrated in the figure. A failure of lip fusion, as shown, may impair the subsequent closure of the palatal shelves, which do not completely fuse until the eighth to ninth week. Thus cleft palate is a frequent association with cleft lip. Other secondary anomalies include defects of tooth development in the area of the cleft lip and incomplete growth of the ala nasa on the side of the cleft. There may be mild ocular hypertelorism, the precise reason for which is undetermined. Tertiary abnormalities can include poor speech and repeated otitis media as a consequence of palatal incompetence.



Left, Normal embryo of 35 days.
Right, Spontaneously aborted 35 day embryo with hypoplasia of the left lateral nasal swelling and, therefore, a cleft lip. 1 – lateral nasal swelling; 2 – maxillary swelling; 3 – medial nasal swelling; 4 – nares; 5 – mandibular swelling. (Courtesy of Prof. G. Töndury, University of Zurich.)

TREACHER COLLINS SYNDROME

(Mandibulofacial Dysostosis, Franceschetti-Klein Syndrome)

Malar Hypoplasia with Downslanting Palpebral Fissures, Defect of Lower Lid, Malformation of External Ear

Although Thomson[1] reported the first case in 1846, the syndrome has been associated with Treacher Collins, who described two cases in 1900. Franceschetti, Zwahlen, and Klein made extensive reports on this condition and called it mandibulofacial dysostosis (1940's). More than 250 cases have been reported.

ABNORMALITIES

Antimongoloid slanting palpebral fissures	89%
Malar hypoplasia	81%
Mandibular hypoplasia	78%
Lower lid coloboma	69%
Partial to total absence of lower eyelashes	53%
Malformation of auricles	77%
External ear canal defect	36%
Conductive deafness	40%
Cleft palate	35%
Projection of scalp hair onto lateral cheek	26%

OCCASIONAL ABNORMALITIES. Coloboma of the upper lid. Microphthalmia. Macrostomia, microstomia, choanal atresia. Blind fistulas and skin tags between auricle and angle of the mouth. Absence of the parotid gland. Congenital heart defect, cervical vertebral anomalies, malformation of the extremities, cryptorchidism. Mental deficiency has been reported in only 5 per cent of the cases.

NATURAL HISTORY. As the great majority of these patients are of normal intelligence, the early recognition of deafness and its correction with hearing aids or surgery, when possible, are of great importance for development.

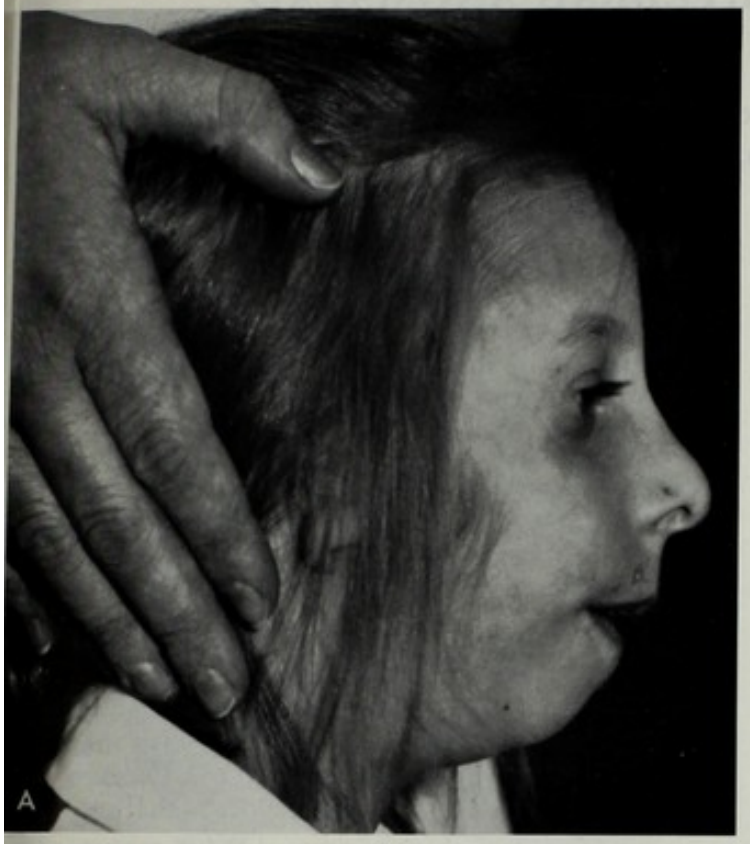
The growth of the facial bones during infancy and childhood results in some cosmetic improvement which may be enhanced by plastic surgery.

ETIOLOGY. Autosomal dominant with 60 per cent of the cases representing presumed fresh mutations. Analysis of affected families shows a regular autosomal dominant inheritance with almost 100 per cent of penetrance. An excess of affected offspring from affected females and of normal offspring from affected males has been found. There is wide variability in expression but moderate similarity within a given sibship.

COMMENT. The wide variance in expression which allows for different clinical forms of the condition has led to erroneous interpretations of some cases, which have been described as separate entities. Franceschetti and Klein have emphasized this phenotypic variability.

REFERENCES

1. Thomson, A.: Notice of several cases of malformation of the external ear, together with experiments on the state of hearing in such persons. Month. J. Med. Sci., *7*:420, 1846.
2. Treacher Collins, E.: Case with symmetrical congenital notches in the outer part of each lower lid and defective development of the malar bones. Trans. Ophthalmol. Soc. U.K., *20*:190, 1900.
3. Franceschetti, A., and Klein, D.: The mandibulofacial dysostosis, a new hereditary syndrome. Copenhagen, E. Munksgaard, 1949.
4. Rovin, S., Dachi, S. F., Borenstein, D. B., and Cotter, W. B.: Mandibulofacial dysostosis, a familial study of five generations. J. Pediatr., *65*:215, 1964.







A, Six year old. Note the hair extending onto the lateral cheek.

B, Preadolescent girl. Note the defect of lower eyelid and the malar hypoplasia.

C, Same as *B*, postadolescent. Note the improvement in cosmetic appearance after a sliding osteotomy to the mandible and plastic surgery to the rudimentary auricle.

FACIO-AURICULO-VERTEBRAL ANOMALAD

(First and Second Branchial Arch Syndrome, Oculoauricular Vertebral Dysplasia, Hemifacial Microsomia, Goldenhar Syndrome)

The predominant defects in this nonrandom association of anomalies represent errors in morphogenesis of the first and second branchial arches, sometimes accompanied by vertebral anomalies and/or ocular anomalies. The occurrence of epibulbar dermoid with this pattern of anomaly, especially when accompanied by vertebral anomaly, was designated as the Goldenhar syndrome, and the predominantly unilateral occurrence was designated as Hemifacial Microsomia. However, the occurrence of various combinations and gradations of this pattern of anomalies, both unilateral and bilateral, with or without epibulbar dermoid, with or without vertebral anomaly, has suggested that Hemifacial Microsomia and the Goldenhar syndrome may simply represent gradations in severity of a similar error in morphogenesis.

ABNORMALITIES. Variable combinations of the following; tending to be *asymmetrical,* 70 per cent unilateral.

Facial. Hypoplasia of malar, maxillary, and/or mandibular region, especially ramus and condyle of mandible and temporomandibular joint. Lateral cleft-like extension of corner of mouth (macrostomia). Hypoplasia of facial musculature.

Ear. Microtia, accessory preauricular tags and/or pits, most commonly in a line from the tragus to the corner of the mouth. Middle ear anomaly with variable deafness.

Oral. Diminished to absent parotid secretion. Anomalies in function or structure of tongue. Malfunction of soft palate.

Vertebral. Hemivertebrae or hypoplasia of vertebrae, most commonly cervical, but may also be thoracic or lumbar.

OCCASIONAL ABNORMALITIES

Eye. Epibulbar dermoid, lipodermoid, notch in upper lid, strabismus, microphthalmia.

Ear. Inner ear defect with deafness.

Oral. Cleft lip, cleft palate.

Cardiac. Ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, and coarctation of aorta, in decreasing order.

Other. Mental deficiency (I.Q. below 85 in 13 per cent). Branchial cleft remnants in anterior-lateral neck, laryngeal anomaly, hypoplasia to aplasia of lung. Occipital encephalocele. Renal anomaly. Limb anomaly. Prenatal growth deficiency. Rib anomaly.

NATURAL HISTORY. Cosmetic surgery is strongly merited. Most of these patients are of normal intelligence. Mental deficiency is more common in association with microphthalmia. Deafness should be excluded at an early age.

ETIOLOGY. Unknown. Usually sporadic. The majority are males (70 per cent), and when unilateral it tends to be right-sided. An occasional relative has similar anomalies. Summitt[8] has reported one family with dominant inheritance of varying degrees of this pattern of anomalies.

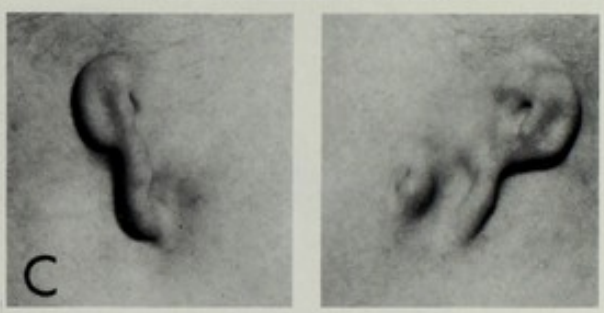
REFERENCES

1. Goldenhar, M.: Associations malformatives de l'oeil et de l'oreille. J. Genet. Hum., *1*:243, 1952.
2. Gorlin, R. J., and Pindborg, J. J.: Oculo-auriculo-vertebral dysplasia. *In* Syndromes of the Head and Neck, by R. J. Gorlin and J. J. Pindborg. New York, McGraw-Hill Book Co., 1964, p. 419.
3. Pashayan, H., Pinsky, L., and Fraser, F. C.: Hemifacial microsomia–oculo-auriculo-vertebral dysplasia. A patient with overlapping features. J. Med. Genet., *7*:185, 1970.
4. Converse, J. M., Coccaro, P. J., Becker, M., and Wood-Smith, D.: On hemifacial microsomia. The first and second branchial arch syndrome. Plast. Reconstr. Surg., *51*:268, 1973.
5. Baum, J. L., and Feingold, M.: Ocular aspects of Goldenhar's syndrome. Am. J. Ophthalmol., *75*:250, 1973.
6. Mellow, D. H., Richardson, J. E., and Douglas, D. M.: Goldenhar's syndrome–oculoauriculo-vertebral dysplasia. Arch. Dis. Child., *48*:537, 1973.
7. Budden, S. S., and Robinson, G. C.: Oculoauricular vertebral dysplasia. Its association with sensorineural deafness and other abnormalities. Am. J. Dis. Child., *125*:431, 1973.
8. Summitt, R. L.: Familial Goldenhar syndrome. Birth Defects, *5*:106, 1969.









A, Right-sided "hemifacial microsomia." Note the macrostomia and micrognathia.

B, Asymmetrical bilateral involvement with left-sided facial weakness. Note the skin tag, which contained cartilage, in the anterior left neck. There were slight epibulbar dermoids, and there was transposition of the great vessels of the heart.

C, Two and one half year old. A laryngeal cyst was excised at four months of age. She has a 40- to 50-decibel hearing deficit by air conduction but normal reception by bone conduction. Note the epibulbar lipodermoids.

VAN DER WOUDE SYNDROME

(Lip Pit–Cleft Lip Syndrome)

Lower Lip Pit(s), +/− Cleft Lip, +/− Missing Second Premolars

Originally reported by Van der Woude[1] in 1954.

ABNORMALITIES

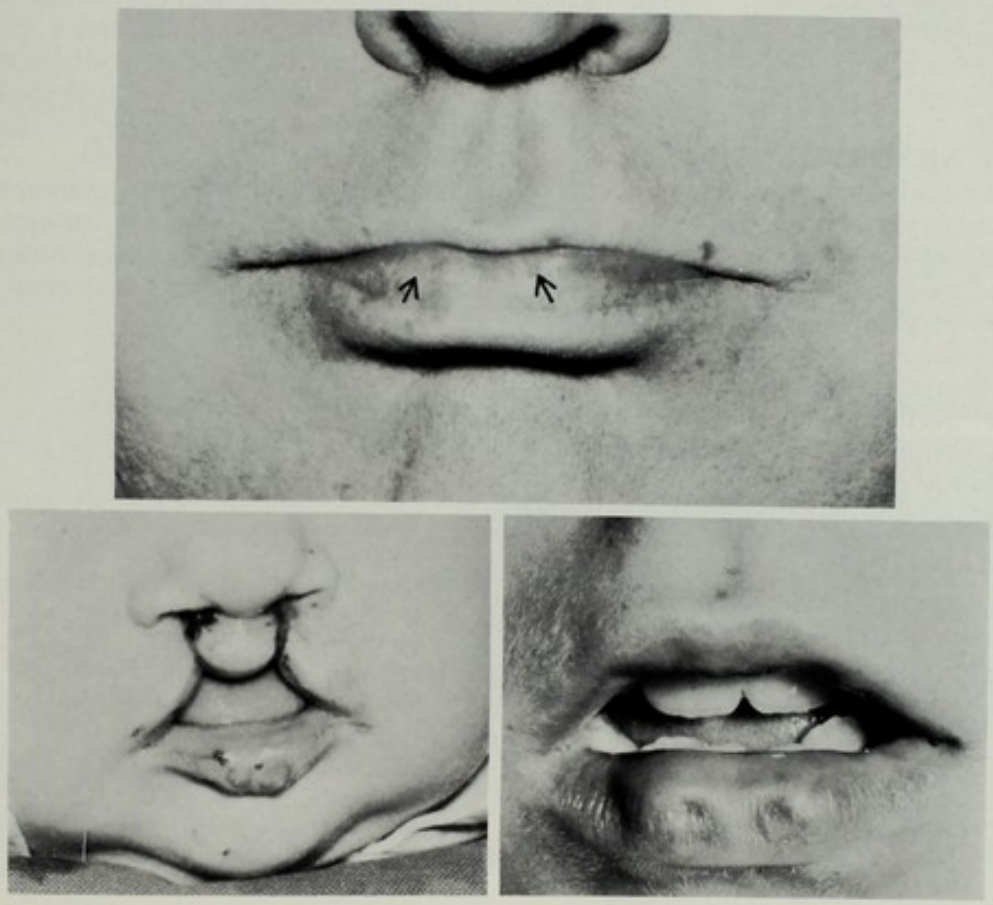
Oral. Lower lip pits (80 per cent).
Hypodontia, missing second premolars.
Cleft lip with or without cleft palate (up to 57 per cent).

NATURAL HISTORY. Surgical removal of the fistulas, which represent accessory small salivary glands, is recommended since they may have a watery mucoid discharge which can be embarrassing for the individual.

ETIOLOGY. Autosomal dominant with about 80 per cent penetrance.

REFERENCES

1. Van der Woude, A.: Fistula labii inferioris congenita and its association with cleft lip and palate. Am. J. Hum. Genet., *6*:244, 1954.
2. Gorlin, R. J., and Pindborg, J. J.: Syndromes of the Head and Neck. New York, McGraw-Hill Book Co., 1963, p. 113.
3. Schneider, E. L.: Lip pits and congenital absence of second premolars: Varied expression of the lip pits syndrome. J. Med. Genet., *10*:346, 1973.



Father and his two sons showing lip pits (denoted by arrows for the father), with cleft lip expression in the infant son.

POPLITEAL WEB SYNDROME

Popliteal Web, Cleft Palate, Lower Lip Pits

This disorder was first reported by Trelat[1] in 1869; about 47 cases have been recorded.

ABNORMALITIES

Oral. Cleft palate with or without cleft lip.
Salivary lower lip pits.

Extremities. Popliteal web, in extreme form from heel to ischium.
Toenail dysplasia.

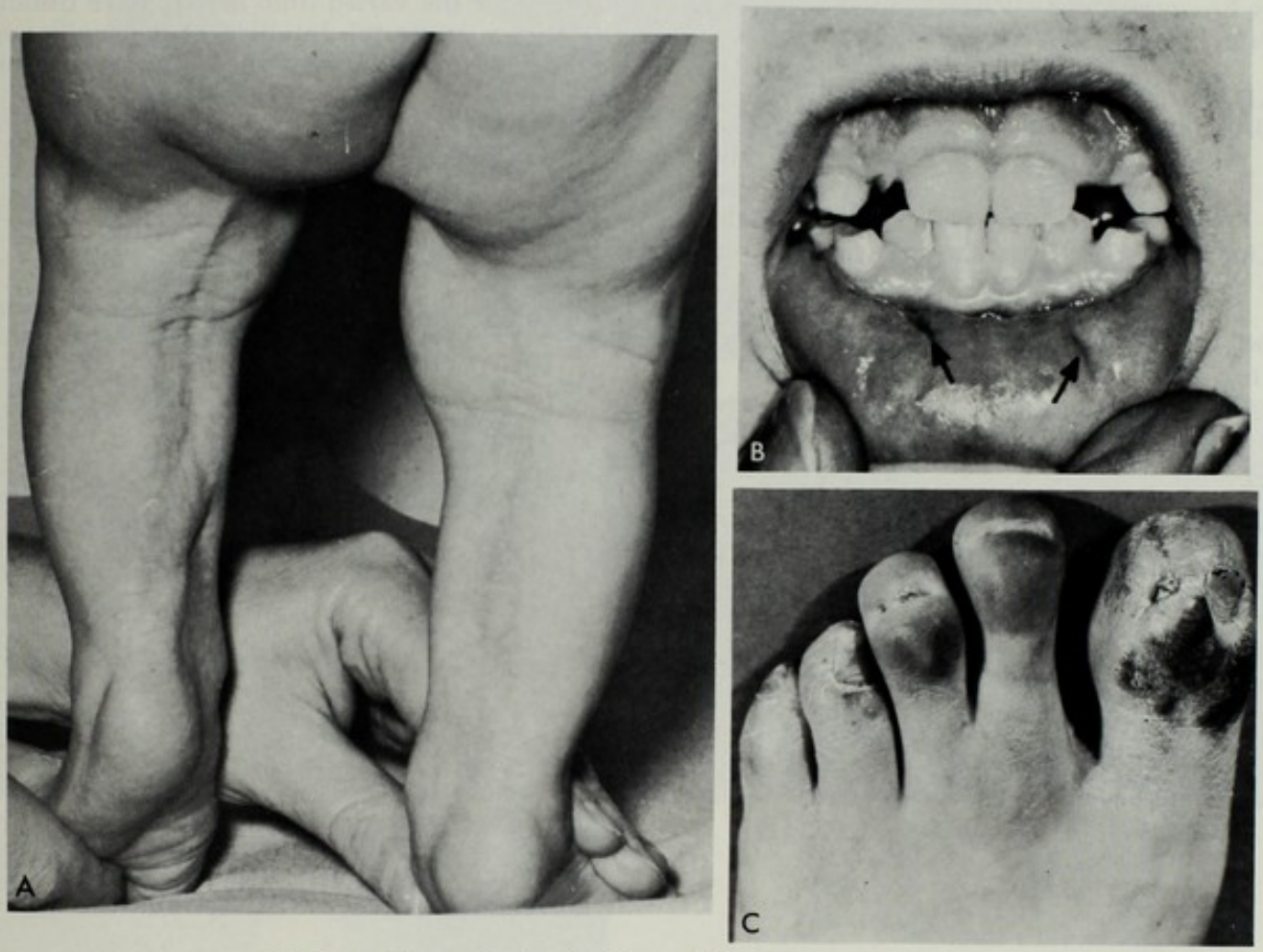
OCCASIONAL ABNORMALITIES. Oral frenula, cutaneous webs between eyelids, intercrural pterygium, syndactyly of fingers or toes, hypoplasia or aplasia of digits, fusion of distal interphalangeal joints, valgus deformity of feet, pyramidal form to skin over hallux, hypoplasia of tibia, bifid or absent patella, posterior dislocation of fibulae, low acetabular angle, spina bifida occulta, other vertebral anomalies, scoliosis, cryptorchidism, bifid scrotum, hypoplastic labia majora, ambiguous external genitalia, inguinal hernia, abnormal scalp hair, mental retardation (two cases).

NATURAL HISTORY. There is usually a dense fibrous cord in the posterior portion of the popliteal pterygium, and extreme care must be exercised in the surgical repair because this cord may contain the tibial nerve. There may be associated defects of muscle in the lower extremities, with limitation of function despite repair of the pterygium. Other webbing across the eyelids or in the mouth may require excision. The palate tends to be short, such that, even with repair of the cleft, function is impaired. Intelligence is usually normal, these individuals are otherwise healthy, and cosmetic and orthopedic corrective procedures are merited.

ETIOLOGY. Autosomal dominant inheritance has been implied. However, autosomal recessive has been implicated in the severe cases, which have occurred in siblings of normal parentage.[3]

REFERENCES

1. Trelat, U.: Sur un vice conformation très-rare de la lèvre-inférieure. J. Med. Chir. Prat., *40*:442, 1869.
2. Hecht, F., and Jarvinen, J. M.: Heritable dysmorphic syndrome with normal intelligence. J. Pediatr., *70*:927, 1967.
3. Bartsocas, C. S., and Papas, C. V.: Popliteal pterygium syndrome. J. Med. Genet., *9*:222, 1972.



A, Infant with popliteal web. Note rod-like taut core.
B, Boy with lower lip pits (arrows).
C, Toenail dysplasia, a variable feature.
(From Hecht, F., and Jarvinen, J. M.: J. Pediatr., *70*:927, 1967.)

HYPOGLOSSIA-HYPODACTYLY SYNDROME

(Aglossia-Adactylia Syndrome)

Hypoglossia, Micrognathia, Hypodactyly

The first case of this disorder was reported by Rosenthal[1] in 1932 and at least 14 cases have subsequently been published.

ABNORMALITIES[2-3]

Orofacial. Recessed mandible, particularly in lower lip region. Hypoplastic lower alveolar ridge with missing teeth. Hypoplasia of tongue with abnormal ventral frenulum.

Limbs. Partial to complete absence of the digits or limbs involving one or more limbs.

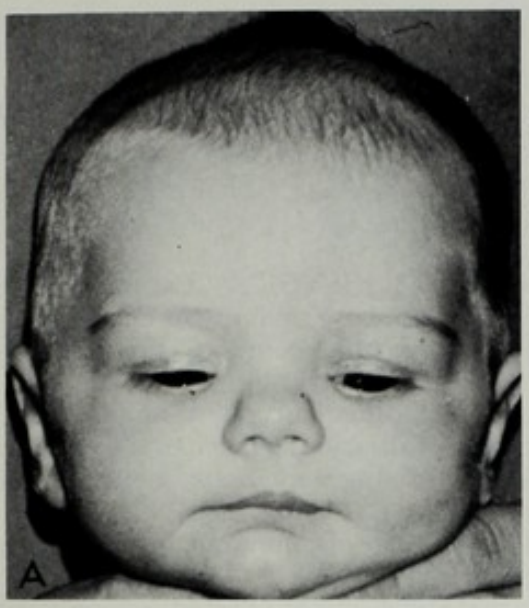
OCCASIONAL ABNORMALITIES. Cleft palate, small oral opening, glossopalatine ankylosis, intral bands and fusion, aberrant alveolar frenulae, hypertrophic sublingual glands, syndactyly.

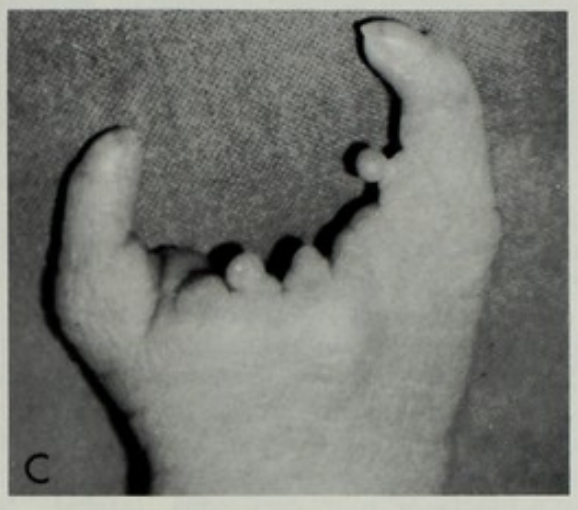
NATURAL HISTORY. Early feeding difficulties are usually mild and transient. Speech development has been surprisingly good. Orthopedic devices for the varied limb defects have usually been very successful. Intelligence is usually normal as is stature (unless there are severe limb deficiencies).

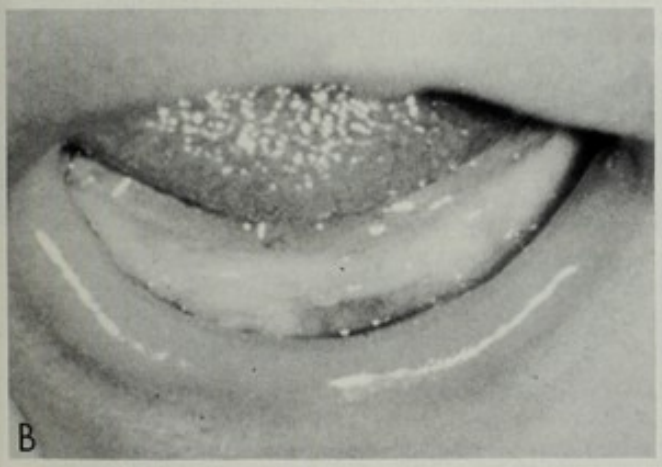
ETIOLOGY. Unknown, sporadic.

REFERENCES

1. Rosenthal, R.: Aglossia congenita. A report of a case of the condition combined with other congenital malformations. Am. J. Dis. Child., *44*:383, 1932.
2. Kelln, E. E., Bennett, C. G., and Klingberg, W. G.: Aglossia-Adactylia syndrome. Am. J. Dis. Child., *116*:549, 1968.
3. Hall, B. D.: Aglossia-Adactylia. A case report, review of the literature, and classification of closely related entities. Birth Defects: Original Article Series *7*(7):233, 1971.











A–D, Young infant showing small mandible and crease below the lower lip, small tongue protruded to its fullest and hypoplastic alveolar ridge, and limb reduction defects. (From Hall, B. D.: Birth Defects: Original Article Series 7(7):233, 1971.)

E, Three year old male showing lower lip indentation and asymmetric hand anomalies.

ORAL-FACIAL-DIGITAL SYNDROME

(OFD Syndrome, Type I)

Oral Frenula and Clefts, Hypoplasia of Alae Nasi, Digital Asymmetry

Papillon-Léage and Psaume[1] set this condition forth as a clinical entity in 1954. More than 130 cases have been reported.

ABNORMALITIES

Oral. Webbing between buccal mucous membrane and alveolar ridge.

Partial clefts in mid-upper lip, tongue, alveolar ridges (at area of lateral incisors which may be missing), between premaxilla and lateral hard palate, with or without irregular complete cleft of soft palate. Dental caries and anomalous anterior teeth.

Facial. Hypoplasia of alar cartilages, lateral placement of inner canthi. Milia of ears and upper face in infancy.

Digital. Asymmetrical shortening of digits with clinodactyly with or without syndactyly.

Scalp. Dry rough hair and dry scalp.

CNS. Variable; mental deficiency in about 57 per cent, with average intelligence quotient of 70.

Cranium. Increased naso-sella-basion angle at base of cranium.

Renal. Autopsy finding of microcysts (7/9).

OCCASIONAL ABNORMALITIES

Oral. Enamel hypoplasia, supernumerary teeth, hamartoma of tongue, fistula in lower lip.

Facial. Frontal bossing, malar hypoplasia, micrognathia.

Digital. Polydactyly foot.

Skeletal. Nonprogressive metaphyseal rarefaction.

CNS. Trembling, hydrocephalus. Seizures. Malformation of brain in 20 per cent of necropsies.

Hair. Alopecia.

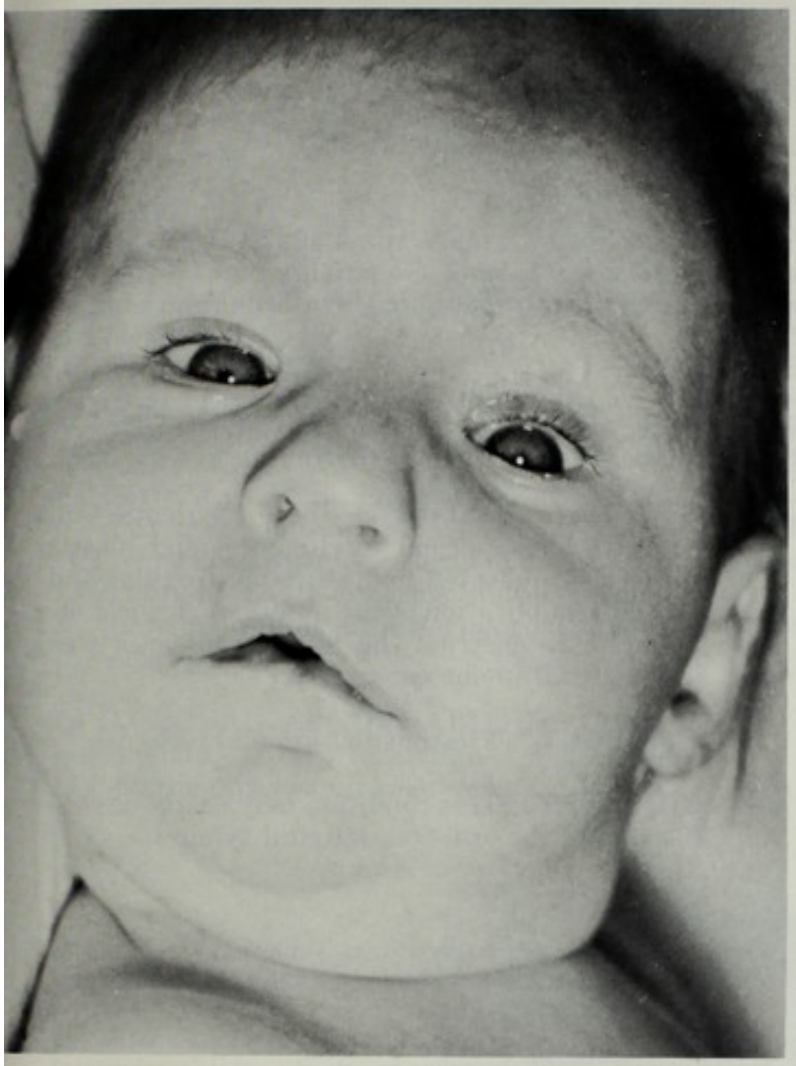
Skin. Granular seborrheic skin.

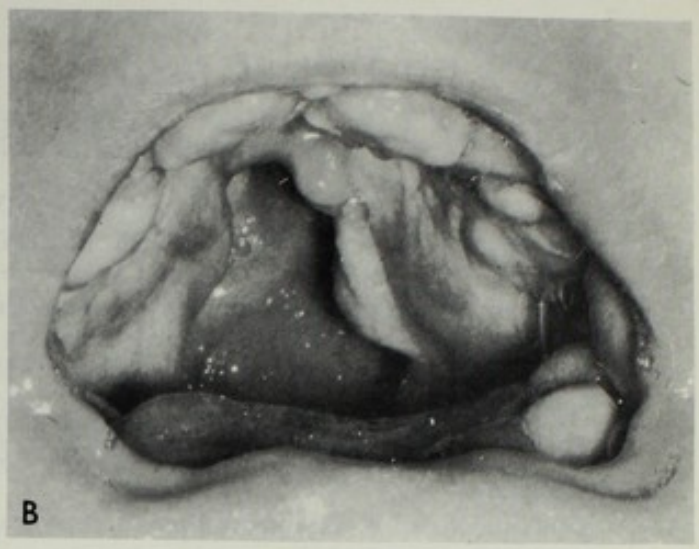
NATURAL HISTORY. Patients may do poorly in early infancy; as many as one third die during this period. Management is directed toward plastic surgical correction of oral clefts and dental care, including dentures when indicated. Psychometric evaluation is merited, because about half the reported patients have mental deficiency.

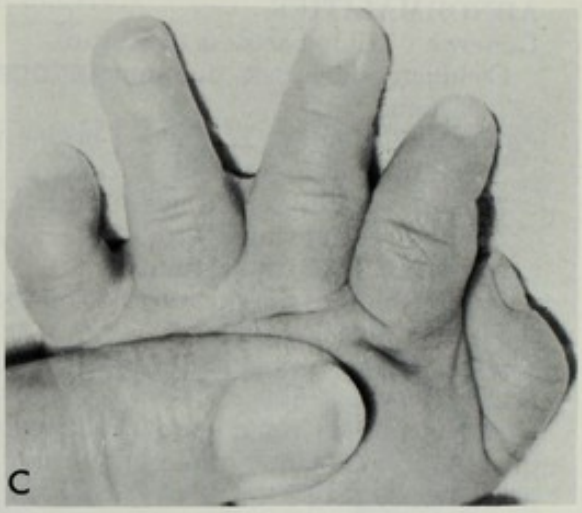
ETIOLOGY. Dominant mutant gene with a lethal effect in the XY male. The ratio of female to male offspring of affected women has been 2:1, and no affected woman has been known to have a son with the OFD syndrome. Therefore the risk for the OFD mother having an affected offspring is one in three. Present data do not allow for a distinction between an X-linked gene, lethal in the hemizygote, and an autosomal mutant which is an early lethal in the male.

REFERENCES

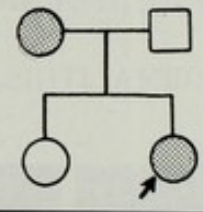
1. Papillon-Léage, Mme., and Psaume, J.: Une malformation héréditaire de la muqueuse buccale: brides et freins anormaux. Rev. Stomatol. (Paris), *55*:209, 1954.
2. Gorlin, R. J., and Psaume, J.: Orodigitofacial dysostosis—a new syndrome. J. Pediatr., *61*:520, 1962.
3. Doege, T. C., Thuline, H. C., Priest, J. H., Norby, D. E., and Bryant, J. S.: Studies of a family with the oral-facial-digital syndrome. N. Engl. J. Med., *271*:1073, 1964.
4. Majowski, F., Lenz, W., Pfeiffer, R. A., and Tünte, W.: Das oro-facio-digitale Syndrom. Symptome und Prognose. Z. Kinderheilkd., *112*:89, 1972.













A, Young infant of a normal mother.
B, Irregular clefts in alveolar ridge, palate, and tongue.
C, Short third finger; partial syndactyly of third and fourth fingers.
D, Seventeen year old daughter of affected mother.

MOHR SYNDROME

(OFD Syndrome, Type II)

Cleft Tongue, Conductive Deafness, Partial Reduplication of Hallux

Mohr[1] described this pattern in several male siblings in 1941, and at least 16 cases have been reported.

ABNORMALITIES

General. Mild shortness of stature.
Conductive deafness due apparently to defect of incus.

Facies and Mouth. Low nasal bridge with lateral displacement of inner canthi.
Broad nasal tip, sometimes slightly bifid.
Midline partial cleft of lip.
Hypertrophy of usual frenula.
Midline cleft of tongue, nodules on tongue.
Flare to alveolar ridge.
Hypoplasia of zygomatic arch, maxilla, and body of mandible.

Limbs. Partial reduplication of hallux, first metatarsal, cuneiform, and cuboid.
Relatively short hands with clinodactyly of fifth finger.
Metaphyseal flaring and irregularity.

OCCASIONAL ABNORMALITIES. Wormian cranial bones, missing central incisors, cleft palate, pectus excavatum, scoliosis.

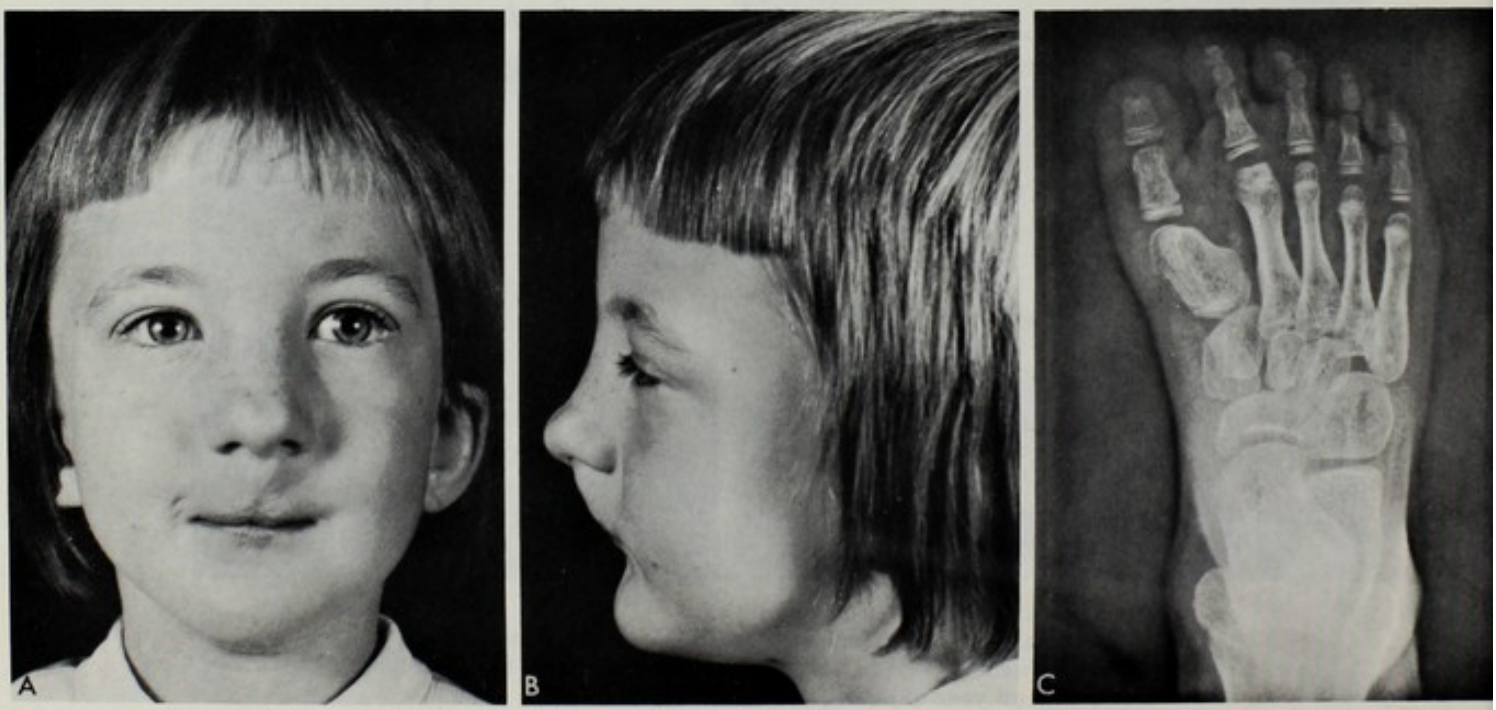
NATURAL HISTORY. These patients apparently have normal intelligence, and plastic surgery is indicated for the clefts, frenula, and partial reduplication of the hallux. A surgical attempt to reconstruct the auditory ossicles was unsuccessful in one case.

ETIOLOGY. Presumed autosomal recessive.

COMMENT. This condition may easily be confused with the oral-facial-digital syndrome.

REFERENCES

1. Mohr, O. L.: A hereditary sublethal syndrome in man. Skr. Norske Vidensk. Akad., I. Mat. Naturv. Klasse, *14*:3, 1941.
2. Rimoin, D. L., and Edgerton, M. T.: Genetic and clinical heterogeneity in the oral-facial-digital syndromes. J. Pediatr., *71*:94, 1967.
3. Pfeiffer, R. A., Majewski, F., and Mannkopf, H.: Das syndrome von Mohr und Claussen. Klin. Paediatr., *184*:224, 1972.



A to *C*, Note the alterations in the upper lip and the aberrant first metatarsal bone. (From Rimoin, D. L., and Edgerton, M. T.: J. Pediatr., *71*:94, 1967.)

MIETENS SYNDROME

Corneal Opacity, Narrow Nose, Flexion Contracture at Elbow

In 1966, Mietens and Weber[1] recorded this pattern of malformation in four of six siblings born of normal unrelated parents.

ABNORMALITIES

General. Dull mentality, with intelligence quotients of 70 to 81.
Small stature.
Facies. Corneal opacity, horizontal and rotatory nystagmus and strabismus.
Narrow nose with hypoplasia of alae nasi.
Extremities. Short forearms and dislocation of proximal radius with flexion contracture at elbow.

OCCASIONAL ABNORMALITIES. Pes valgus, inability to fully extend knee, dislocation of hip, pectus excavatum, aneurysm.

NATURAL HISTORY. Because of the impaired vision plus the limitation of function of the arms, it is difficult to know whether the 70 to 80 intelligence quotients are a valid indicator of mental defect or not. Vascular anomalies may be a serious feature in this syndrome. The older girl (illustration) died from rupture of an aneurysm of the right anterior cerebral artery.[2]

ETIOLOGY. Undetermined. ? Autosomal recessive.

REFERENCES

1. Mietens, C., and Weber, H.: A syndrome characterized by corneal opacity, nystagmus, flexion contracture of the elbows, growth failure, and mental retardation. J. Pediatr., *69*:624, 1966.
2. Mietens, C.: Personal communication.



Affected siblings. Note the hypoplasia of the alae nasi and the position of the dislocated elbows. (From Mietens, C., and Weber, H.: J. Pediatr., *69*:624, 1966.)

OCULODENTODIGITAL SYNDROME

Microphthalmos, Enamel Hypoplasia, Camptodactyly of Fifth Fingers

Originally described in 1920 by Lohmann,[1] this pattern was more fully characterized by Gorlin, Meskin, and St. Geme[2] in 1963.

ABNORMALITIES

Eye. Microphthalmos, microcornea, fine porous iris.

Nose. Thin, hypoplastic alae nasi with small nares.

Teeth. Enamel hypoplasia.

Hands and Feet. Syndactyly of fourth and fifth fingers, third and fourth toes. Camptodactyly of fifth fingers. Midphalangeal hypoplasia or aplasia of one or more fingers, toes.

Hair. Fine, dry, and/or sparse and slow growing.

Other Skeletal. Broad tubular bones and mandible with wide alveolar ridge.

OCCASIONAL ABNORMALITIES. Small palpebral fissures, epicanthic folds, glaucoma, partial anodontia, microdontia, premature loss of teeth, cleft lip and palate, conductive hearing impairment, cubitus valgus, hip dislocation, osteopetrosis, poor posture.

NATURAL HISTORY. Inadequate information. Mentally normal.

ETIOLOGY. Autosomal dominant with variable expressivity; many cases represent fresh mutations.

REFERENCES

1. Lohmann, W.: Beitrag zur Kenntnis des reinen Mikrophthalmus. Arch. Augenh., *86*:136, 1920.
2. Gorlin, R. J., Meskin, L. H., and St. Geme, J. W.: Oculodentodigital dysplasia. J. Pediatr., *63*:69, 1963.
3. Gillespie, F. D.: A hereditary syndrome: "dysplasia oculodentodigitalis." Arch. Ophth., *71*:187, 1964.
4. Eidelman, E., Chosack, A., and Wagner, M. L.: Orodigitofacial dysostosis and oculodentodigital dysplasia. Two distinct syndromes with some similarities. Oral Surg., *23*:311, 1967.



Twelve year old. Note the microcornea, small eyes, hypoplasia of the alae nasi, camptodactyly, repaired syndactyly of the fourth and fifth fingers, and bony abnormalities. (From Gorlin, R. J., et al.: J. Pediatr., *63*:69, 1963.)

OTO-PALATO-DIGITAL SYNDROME

(Taybi Syndrome)

Deafness, Cleft Palate, Broad Distal Digits with Short Nails

Initially described by Taybi in 1962, many cases have subsequently been recognized.

ABNORMALITIES

Performance. Mild mental deficiency; I.Q., 75 to 90.

Growth. Small stature, all below tenth percentile for age.

Hearing. Moderate conductive deafness.

Cranium. Frontal and occipital prominence with thick frontal bone and thick base of skull having a steep naso-basal angulation. Absence of frontal and sphenoid sinuses.

Facies. Facial bone hypoplasia and hypertelorism with small nose and mouth, but lateral fullness of the supraorbital ridges.

Mouth. Partial anodontia, impacted teeth, or both. Cleft soft palate, small tonsils.

Midskeletal. Small trunk, pectus excavatum, failure of neural arch fusion, small iliac crests.

Limbs. Limited elbow extension, inward bowing tibiae. Short broad distal phalanges of thumbs and toes, to a lesser extent for other digits, with short nails. Relatively short third, fourth, fifth metacarpals. Fusion of hamate and capitate. Accessory ossification center at the base of the second metatarsal.

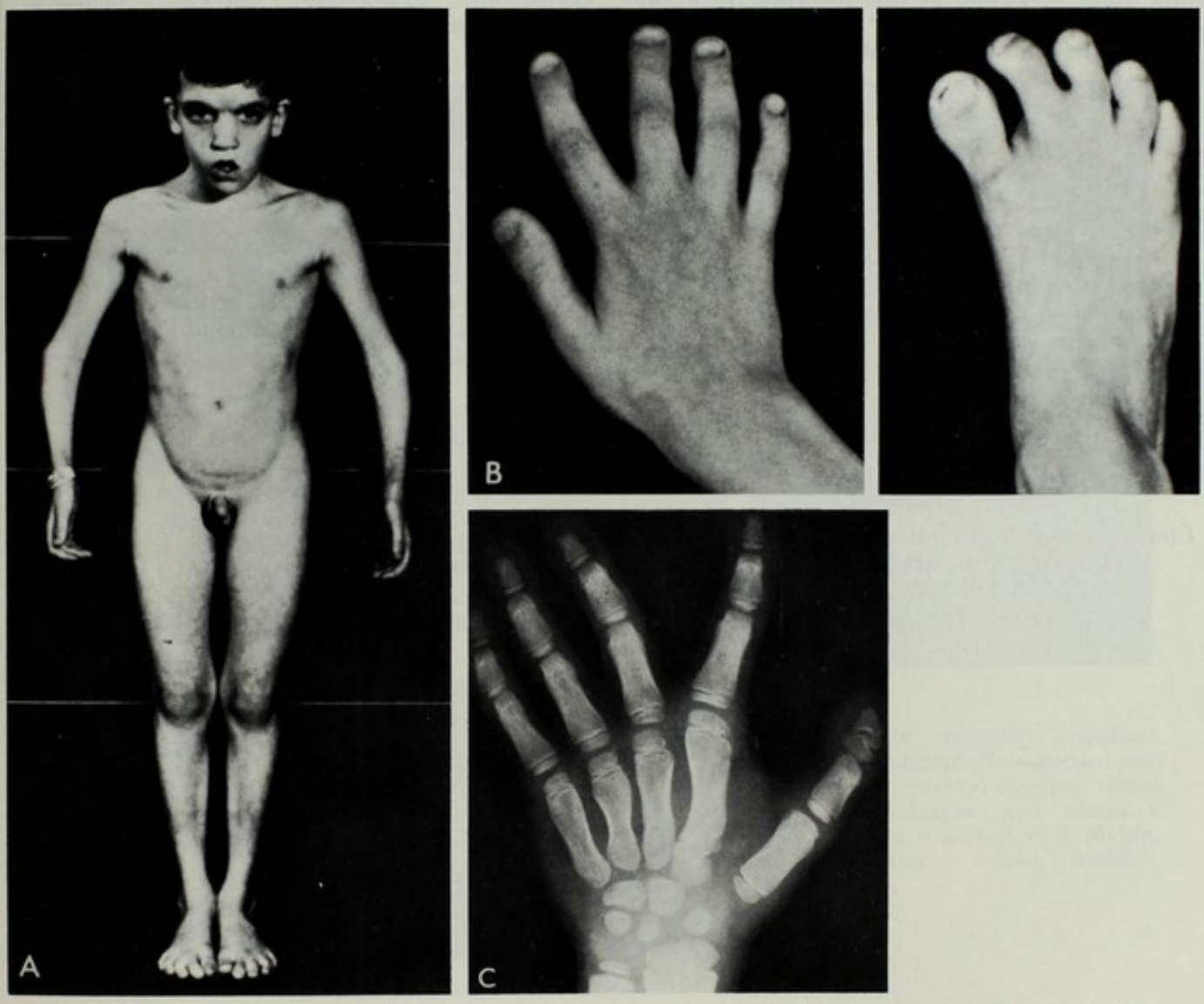
OCCASIONAL ABNORMALITIES. Delayed closure of anterior fontanel, hip dislocation, limited knee flexion, syndactyly of toes, hallucal nail dystrophy.

NATURAL HISTORY. Speech development is retarded on the basis of hearing impairment, mental deficiency, or both.

ETIOLOGY. X-linked semidominant. Females show mild to almost full expression, especially the fullness of the lateral supraorbital ridges, short nails, clinodactyly of toes, and roentgenographic abnormalities in limbs and skull.

REFERENCES

1. Taybi, H.: Generalized skeletal dysplasia with multiple anomalies. Am. J. Roentgenol. Radium Ther. Nucl. Med., *88*:450, 1962.
2. Dudding, B. A., Gorlin, R. J., and Langer, L. O.: The oto-palato-digital syndrome. A new symptom-complex consisting of deafness, dwarfism, cleft palate, characteristic facies, and a generalized bone dysplasia. Am. J. Dis. Child., *113*:214, 1967.
3. Gorlin, R. J., Poznanski, A. K., and Hendon, I.: The oto-palato-digital (OPD) syndrome in females. Oral Surg., *35*:218, 1973.



A to *C*, Note irregular length and form of distal phalanges, especially thumb. (From Dudding, B. A., Gorlin, R. J., and Langer, L. O.: Am. J. Dis. Child., *113*:214, 1967.)

COFFIN-LOWRY SYNDROME

Downslanting Palpebral Fissures, Bulbous Nose, Tapering Fingers

Coffin[1] reported two affected males in 1966 and other instances of this disorder have subsequently been recognized.[2] The facies may appear similar to that of the Williams syndrome.

ABNORMALITIES

Growth. Mild to moderate growth deficiency, apparently of postnatal onset.

Performance. Mental deficiency, usually severe. Relative weakness.

Facies. Coarse appearance with downslanting palpebral fissures and maxillary hypoplasia, mild hypertelorism, prominent brow, and broad nose with thick alae nasae and septum.

Thorax. Short bifid sternum with pectus carinatum.

Spine. Anterior superior marginal vertebral defects, thoracolumbar scoliosis.

Limbs. Large soft hands with tapering fingers and tufted drumstick roentgenogram appearance to distal phalanges. Accessory thenar crease. Flat feet. Lax ligaments.

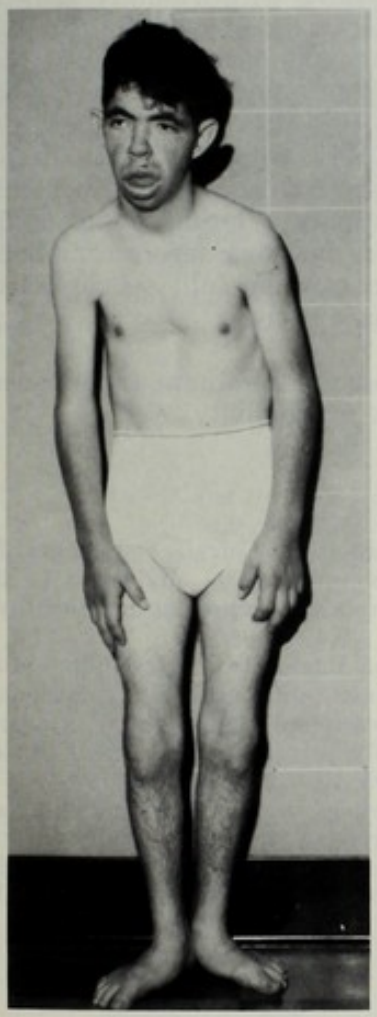
OCCASIONAL ABNORMALITIES. Thick calvarium, hypoplastic sinuses, mastoids. Simian crease.

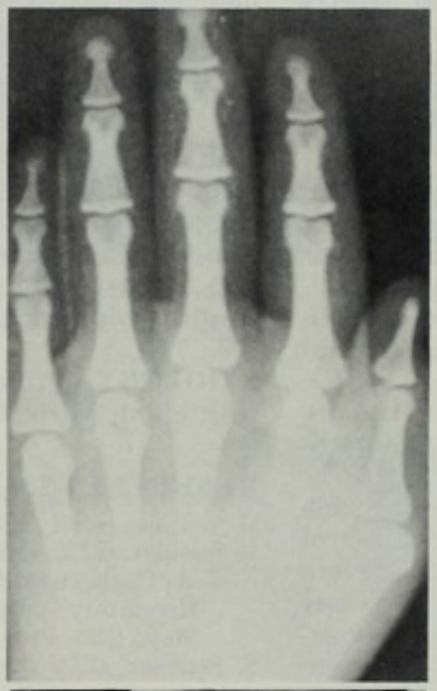
NATURAL HISTORY. The mental deficiency is usually of severe degree, without speech. The stooped posture and evidences of muscle weakness suggest a problem of muscle function in this disorder.

ETIOLOGY. X-linked semidominant inheritance is implied, with striking similarity between the severely affected hemizygous males and variable mild features, including the tufted distal phalanges, in the carrier females.

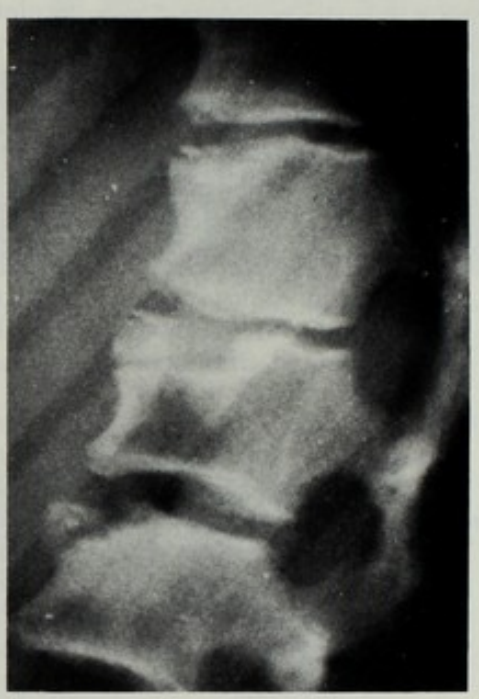
REFERENCES

1. Coffin, G. S., Siris, E., and Wegienka, L. C.: Mental retardation with osteocartilaginous anomalies. Am. J. Dis. Child., *112*:205, 1966.
2. Procopis, P. G., and Turner, B.: Mental retardation, abnormal fingers, and skeletal anomalies: Coffin's syndrome. Am. J. Dis. Child., *124*:258, 1972.









Seriously mentally deficient young adult patient. Note stooped posture, facies, vertebral changes, tufted terminal phalanges, and accessory thenar crease. (Courtesy of S. Myhre, Rainier Training School, Buckley, Washington.)

STICKLER SYNDROME

(Hereditary Arthro-Ophthalmopathy)

Flat Facies, Myopia, Spondyloepiphyseal Dysplasia

Stickler, et al.[1, 2] reported the initial observations in 1965 on affected individuals in five generations of one family; the skeletal aspects have been further documented by Spranger[3] and the total spectrum of the disorder has been set forth by Hermann, et al.[4]

ABNORMALITIES

Orofacial. Flat facies with depressed nasal bridge and epicanthal folds, midfacial or mandibular hypoplasia, clefts of hard and/or soft palate and occasionally of uvula, micrognathia, Robin anomalad, deafness (both sensorineural and conductive), and dental anomalies.

Ocular. Myopia (8 to 18 diopters) usually present before the age of ten, retinal detachment and/or cataracts.

Musculo-Skeletal. Hypotonia, hyperextensible joints, Marfanoid habitus. Prominence of large joints may be present at birth. Severe arthropathy can occur in childhood. Lesser joint pains simulate juvenile rheumatoid arthritis. Subluxation of hip. Mild to moderate spondyloepiphyseal dysplasia, i.e., flat vertebrae with anterior wedging and underdevelopment of the distal tibial epiphyses. Long bones show disproportionately narrow shafts relative to their metaphyseal width.

OCCASIONAL ABNORMALITIES. Scoliosis, mental deficiency.

COMMENT. The Stickler syndrome should be considered in any newborn with the Robin anomalad, particularly those with a family history of cleft palate and in patients with dominantly inherited myopia, nontraumatic retinal detachment, and/or mild spondyloepiphyseal dysplasia.

NATURAL HISTORY. There is little documented evidence for progression of either the myopia or the arthropathy. Retinal detachment leading to blindness, the most severe complication of this disorder, can hopefully be corrected surgically if recognized early.

ETIOLOGY. Autosomal dominant inheritance with highly variable expressivity.

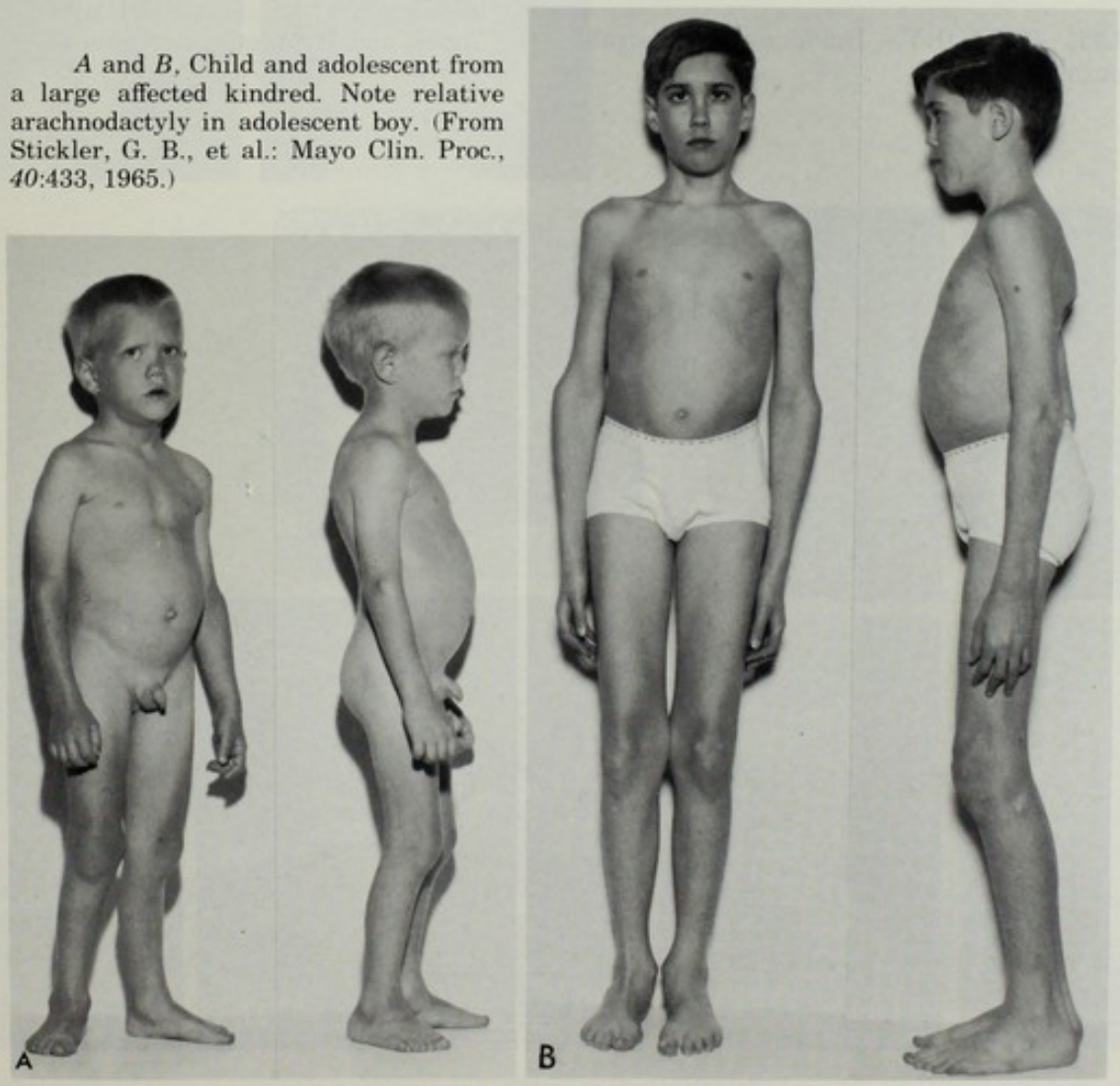
REFERENCES

1. Stickler, G. B., Belau, P. G., Farrell, F. J., Jones, J. D., Pugh, D. G., Steinberg, A. G., and Ward, L. E.: Hereditary progressive arthro-ophthalmopathy. Mayo Clin. Proc., *40*:433, 1965.
2. Stickler, G. B., and Pugh, D. G.: Hereditary progressive arthro-ophthalmopathy. II. Additional observations on vertebral abnormalities, a hearing defect, and a report of a similar case. Mayo Clin. Proc., *42*:495, 1967.
3. Spranger, J.: Arthro-ophthalmopathia hereditaria. Ann. Radiol. (Paris), *11*:359, 1968.
4. Hermann, J., et al.: The Stickler syndrome (hereditary arthroophthalmopathy. Birth Defects, *11*(2): 76, 1975.



Girl showing flat facies, inner canthal folds, relatively narrow diaphyses and hamate-capitate carpal synostosis. (From Dr. Judith Hall, University of Washington.)

A and *B*, Child and adolescent from a large affected kindred. Note relative arachnodactyly in adolescent boy. (From Stickler, G. B., et al.: Mayo Clin. Proc., *40*:433, 1965.)



LARSEN SYNDROME

Multiple Joint Dislocation, Flat Facies, Short Fingernails

Larsen, Schottstaedt, and Bost[1] described six sporadic cases of this condition in 1950.

ABNORMALITIES

Facies. Flat, with depressed nasal bridge and prominent forehead, hypertelorism.

Joints. Dislocations of elbows, hips, and knees.

Hands. Spatulate thumbs, short nails, shortened metacarpals, multiple carpal ossification centers.

Feet. Equinovalgus or varus. Delayed coalescence of the two calcaneal ossification centers.

OCCASIONAL ABNORMALITIES. Cleft palate and/or lip, abnormal segmentation of cervical vertebrae, scoliosis.

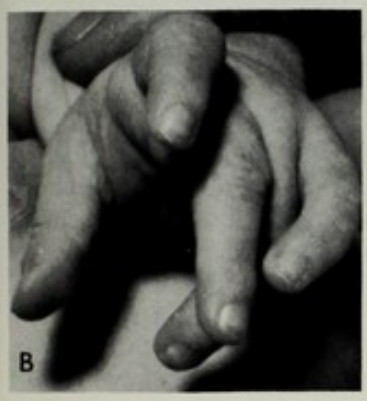
NATURAL HISTORY. Inadequate information. Mentally normal.

ETIOLOGY. Unknown. Autosomal dominant inheritance is indicated by one of the original patients reported by Larsen having had an affected child.

REFERENCES

1. Larsen, L. J., Schottstaedt, E. R., and Bost, F. C.: Multiple congenital dislocations associated with characteristic facial abnormality. J. Pediatr., *37*:574, 1950.
2. Latta, R. J., Graham, C. B., Aase, J., Scham, S. M., and Smith, D. W.: Larsen's syndrome: A skeletal dysplasia with multiple joint dislocations and unusual facies. J. Pediatr., *78*:291, 1971.
3. Silverman, F. N.: Larsen's syndrome: Congenital dislocation of the knees and joints, distinctive facies, and, frequently, cleft palate. Ann. Radiol. (Paris), *15*:297, 1972.







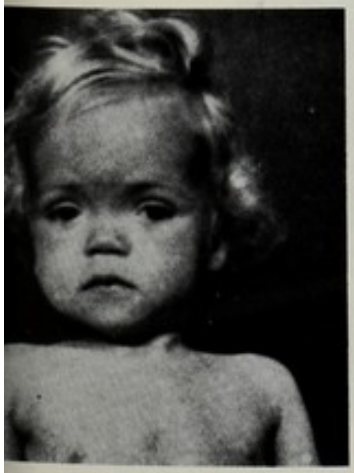
A to *D*, Two week old with dislocations of elbow, hip, and knee; altered hand positioning and short metacarpals; and flat facies.

E and *F*, Features from patients described by Larson, et al.: J. Pediatr., *37*:574, 1950.















LANGER-GIEDION SYNDROME

(Langer-Giedion Type of Tricho-Rhino-Phalangeal Syndrome)

Multiple Exostoses, Bulbous Nose with Peculiar Facies, Loose Redundant Skin in Infancy

Hall, et al.[1] in 1972 reported five new cases of this disorder and included two further sporadic cases from the literature.[2-4] While the facies of these patients resemble that of the Tricho-Rhino-Phalangeal syndrome, other features allow for separation of the two syndromes.

ABNORMALITIES. Based on seven patients.[1]

Growth. Mild postnatal onset of growth deficiency.

Performance. Mild to moderate mental deficiency.

Cranium. Mild microcephaly.

Facies. Large laterally protruding ears, full to heavy eyebrows, large bulbous nose with thickened alae and septum and dorsally tented nares, simple philtrum which is prominent and elongated, thin upper lip, and recessed mandible.

Hair. Sparse scalp hair.

Skin. Redundancy and/or looseness in infancy which regresses with age. Maculopapular nevi about the scalp, facies, neck, upper trunk, and upper limbs.

Hands. Cone-shaped epiphyses which become radiologically evident around three to four years of age, lack of normal modeling in metaphyseal regions, poor funnelization at proximal ends of phalanges, metaphyseal hooking over the lateral edges of the cone-shaped epiphyses, and exostoses.

Long Tubular Bones. Multiple exostoses with time of onset and distribution similar to the autosomal dominant variety of multiple cartilaginous exostoses. Exostoses can involve other areas such as the ribs, scapulae, and pelvic bones.

Other. Tendency toward fractures, winged scapulae, lax joints, hypotonia, exotropia, recurrent upper respiratory tract infections, disproportionate delay in the onset of speech.

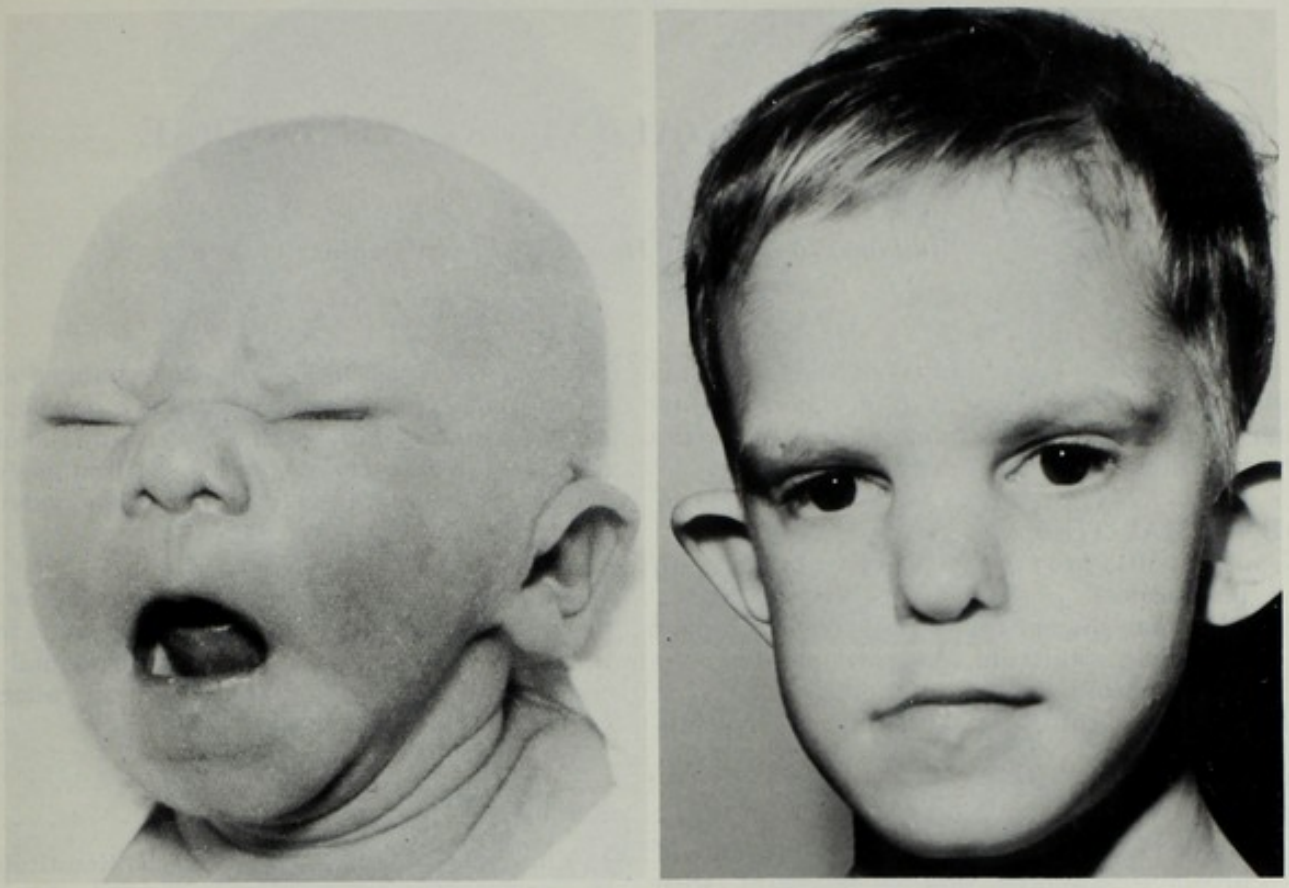
OCCASIONAL ABNORMALITIES. Deafness, hypochromic anemia, thin hypomineralized bones, clinobrachydactyly, bowed femora, hernias.

NATURAL HISTORY. Some of these children have such redundance and/or looseness to their skin at birth that are misdiagnosed as having the Ehlers-Danlos syndrome. Recurrent respiratory tract infections during the first four to five years. General health is usually good after that except for a tendency toward fractures and the usual problems of multiple exostoses with its variable effects on bone growth.

ETIOLOGY. Unknown, sporadic.

REFERENCE

1. Hall, B. D., et al.: Langer-Giedion syndrome. Birth Defects, *10*(12):147, 1974.



Patient as newborn and at seven years. Note the sparseness of hair, bulbous nose, simple but prominent philtrum, and redundant folds of skin on the neck, superiorly tented nares, thin upper lip, and prominent ears.



Eleven and one half year old, showing exostoses, cone-shaped epiphyses, and metaphyseal hooking at the proximal ends of a number of the middle phalanges.

TRICHO-RHINO-PHALANGEAL SYNDROME

Bulbous Nose, Sparse Hair, Epiphyseal Coning

Klingmuller[1] reported two siblings with this pattern of malformation in 1956. Giedion[2] further established the syndrome and set forth the Tricho-Rhino-Phalangeal designation for it.

ABNORMALITIES[1-4]

Growth. Mild growth deficiency (third to tenth percentiles).

Facial. Pear-shaped appearing nose, prominent and long philtrum, narrow palate, +/− micrognathia, large prominent ears.

Skin. Sparse, thin hair with relative hypopigmentation.

Nails. Thin.

Skeletal. Short metacarpals, metatarsals, especially fourth and fifth. Development of broadened middle phalangeal joint with cone-shaped epiphyses, especially second through fourth fingers and toes. Aberrant angulation of tapering distal fingers. Short distal phalanges of thumb, toe. Split distal radial epiphysis. Winged scapulae.

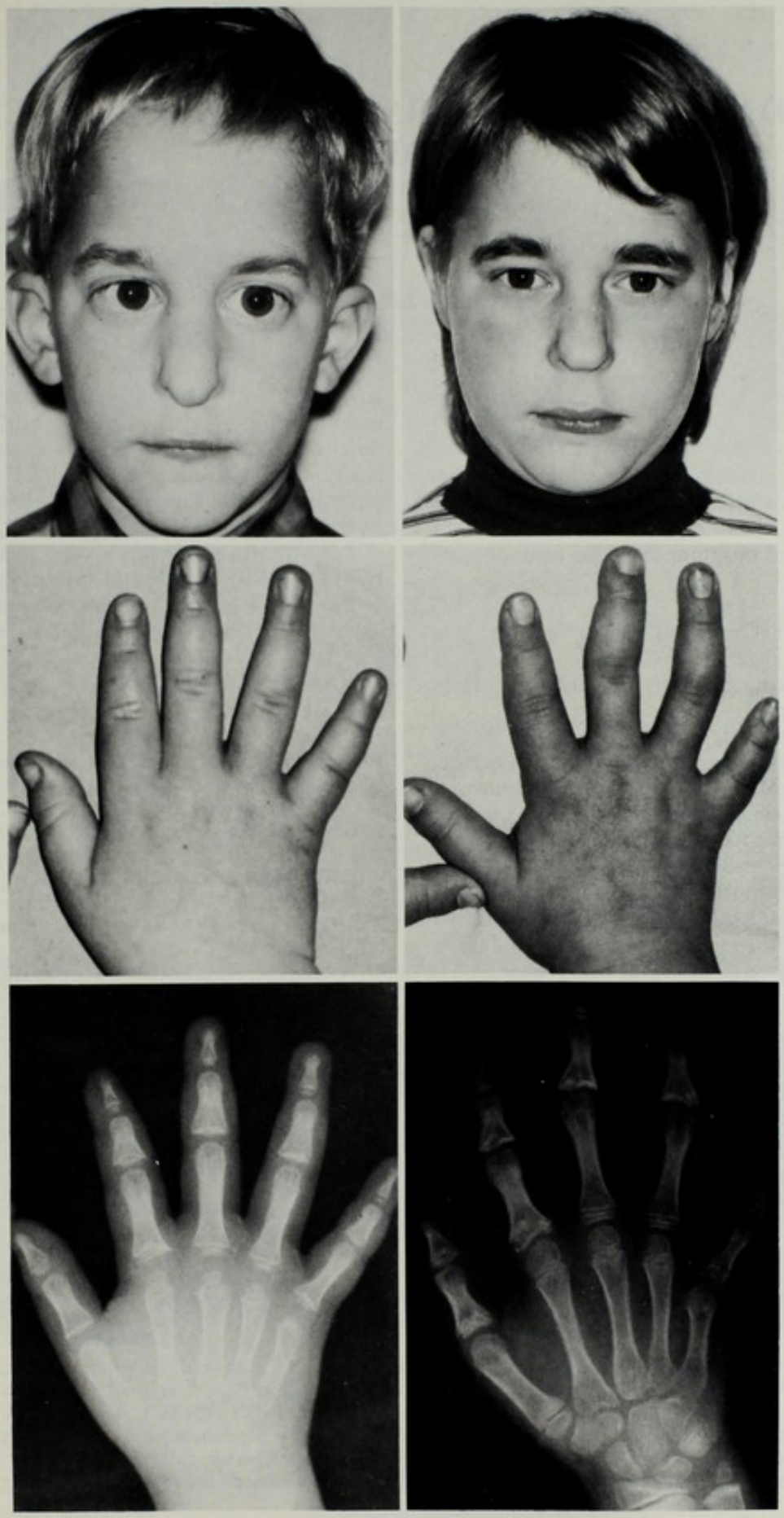
OCCASIONAL ABNORMALITIES. Mild metaphyseal exostoses, femoral head dysplasia (Legg-Perthe-like), scoliosis, pes planus, short stature, mental deficiency.

NATURAL HISTORY. Osseous changes such as the cone-shaped epiphyses may develop in early childhood and become worse until adolescent growth is complete. Increased frequency of upper respiratory infections has been noted in some cases.

ETIOLOGY. Heterogeneity is suggested by autosomal dominant-type inheritance in some families[4] (the great majority), while autosomal recessive inheritance is suggested in affected sibships of normal parentage.[1]

REFERENCES

1. Klingmuller, G.: Über eigentumliche Konstitutionsanomalien bei 2 Schwestern und ihre Beziehungen zu neueren entwicklungspathologischen Befunden. Hautarzt, *7*:105, 1956.
2. Giedion, A.: Das tricho-rhino-phalangeale Syndrom. Helv. Paediatr. Acta, *21*:475, 1966.
3. Gorlin, R. J., Cohen, M. M., and Wolfson, J.: Tricho-rhino-phalangeal syndrome. Am. J. Dis. Child., *118*:595, 1969.
4. Fontaine, G., Maroteaux, P., Farriaux, J.-P., Richard, J., and Roellens, B.: Le syndrome tricho-rhino-phalangien. Arch. Fr. Pediatr., *27*:635, 1970.



Six year old son *(left)* and nine year old daughter *(right)* of an affected father who became bald at 21 years of age. The children have fine, slow-growing hair. Note the tented hypoplastic nares, prominent philtrum, and the asymmetric length of fingers related to radiographic evidence of irregular metaphyseal cupping with cone-shaped epiphyses. (Courtesy of D. Weaver, University of Washington, Seattle.)

ECTRODACTYLY–ECTODERMAL DYSPLASIA–CLEFTING SYNDROME

(EEC Syndrome)

Ectrodactyly, Ectodermal Dysplasia, Cleft Lip-Palate

Although the association of ectrodactyly and cleft lip had been noted, it was not until 1970 that Rüdiger, et al.[1] appreciated that at least some of these patients also had features of ectodermal dysplasia, and named the disorder the EEC syndrome. Bixler, et al.[2] added two additional cases and summarized the past observations.

ABNORMALITIES.[1] All features are variable.

Skin. Fair, thin, mild hyperkeratosis. Hypoplastic nipples.

Hair. Light-colored, sparse, thin, wiry.

Teeth. Partial anodontia, microdontia, carious.

Eyes. Blue irides, photophobia, blepharophimosis, atresia or defects of lacrimal duct system. Blepharitis and dacharocystitis.

Face. Cleft lip, ±cleft palate, maxillary hypoplasia, mild malar hypoplasia.

Limbs. Defects in midportion of hands and feet varying from syndactyly to ectrodactyly. Mild nail dysplasia.

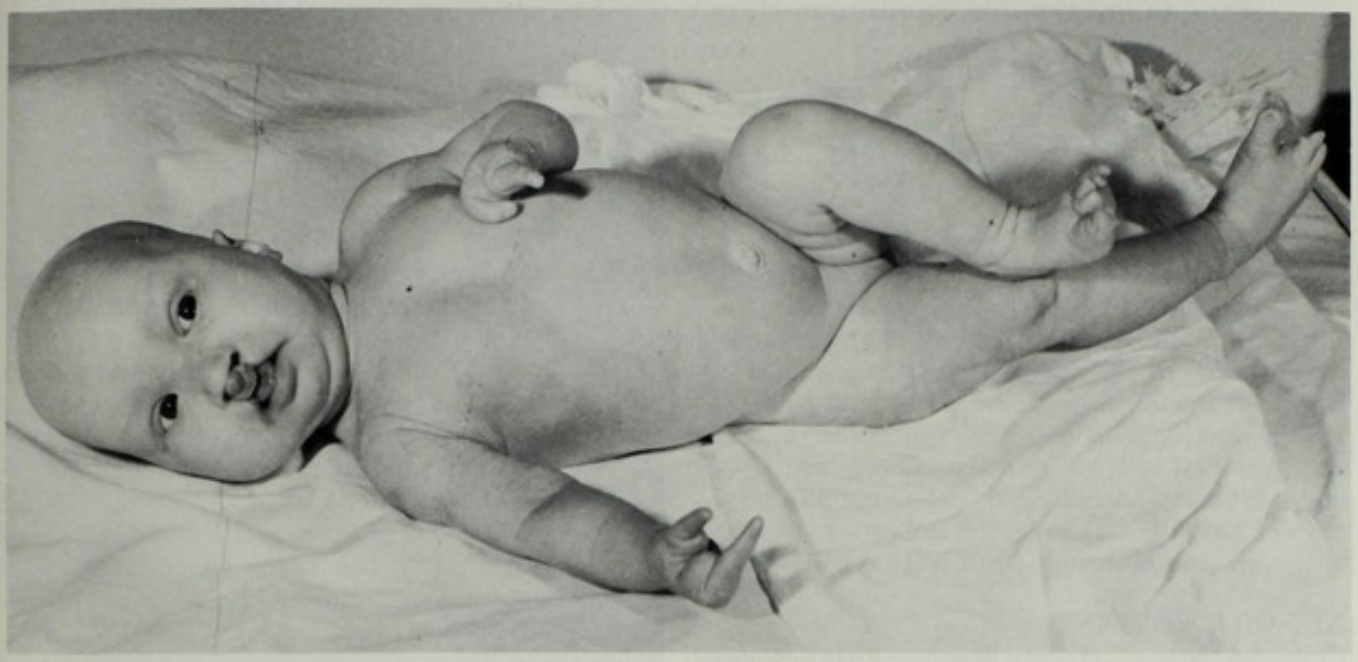
OCCASIONAL ABNORMALITIES. Deafness, small or malformed auricles, renal anomaly.

NATURAL HISTORY. These individuals are usually of normal intelligence and adapt reasonably well in life with surgical closure of the facial clefts plus the variable need for limb surgery, dentures, and wigs. Early and continued ophthalmologic evaluation and management for the defective lacrimal duct system is imperative, since chronic dacrocystitis with corneal scarring can be the major debilitating problem in this disorder.

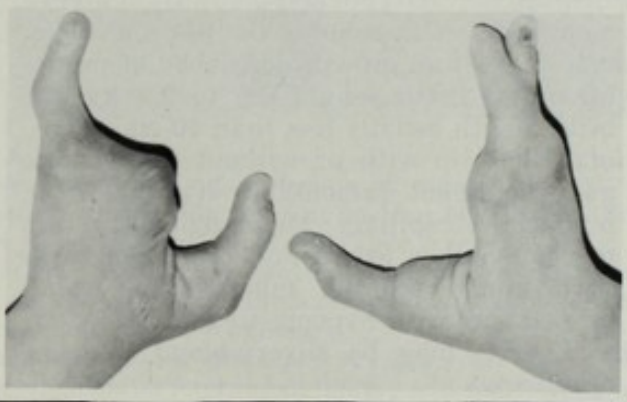
ETIOLOGY. Autosomal dominant inheritance is implied[3, 4] with variable expression and even lack of penetrance being noted in some families.

REFERENCES

1. Rüdiger, R. A., Haase, W., and Passarge, E.: Association of ectrodactyly, ectodermal dysplasia, and cleft lip-palate. Am. J. Dis. Child., *120*:160, 1970.
2. Bixler, D., Spivack, J., Bennett, J., and Christian, J. C.: The ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. Clin. Genet., *3*:43, 1972.
3. Cockayne, E. A.: Cleft palate, hare lip, dacryocystitis and cleft hand and feet. Biometrika, *28*:60, 1936.
4. Walker, J. C., and Clodius, L.: The syndromes of cleft lip, cleft palate and lobster-claw deformities of hands and feet. Plast. Reconstr. Surg., *32*:627, 1963.
5. Robinson, G. C., Wildervanck, L. S., and Chiang, T. P.: Ectrodactyly, ectodermal dysplasia, and cleft lip-palate syndrome. J. Pediatr., *82*:107, 1973.
6. Kaiser-Kupfer, M.: Ectrodactyly, ectodermal dysplasia and clefting syndrome. Am. J. Ophthalmol., *76*:992, 1973.









Above, Six month old with thin, dry, lightly pigmented skin, sparse, fine hair, photophobia with inflammation of conjuctiva, and small ears. Note the intraindividual variability of anomaly in the feet. (From Rüdiger, R. A., et al.: Am. J. Dis. Child., *120:*160, 1970. Courtesy of E. Passarge.)

Below, Eighteen year old (wearing a wig) with coarse, sparse hair who has photophobia and blepharophimosis and only five poorly developed teeth. Note the small melanomata in the thin skin, which shows patchy areas of dermatitis. Studies revealed absence of the right kidney with a double collecting system on the left.

ROBERTS SYNDROME

(Pseudothalidomide Syndrome, Hypomelia-Hypotrichosis-Facial Hemangioma Syndrome)

Hypomelia, Mid-Facial Defect, Severe Growth Deficiency

This disorder was initially described by Roberts[1] in 1919 and more recently by Appelt, et al.[2] Freeman, et al.[3] reported five cases and reviewed the features in the 17 previously recognized patients. The cases reported by Herrmann, et al.[4] as "Pseudothalidomide or SC syndrome" and the case reported by Hall and Greenberg[5] as "Hypomelia-Hypotrichosis-Facial hemangioma syndrome" may be examples of Roberts syndrome, although this question is not fully resolved.

ABNORMALITIES[1–5]

Performance. Microbrachycephaly. Severe mental defect in some of the few survivors.

Growth. Profound growth deficiency of prenatal onset. Birth weight 1.5 to 2.2 kg and birth length usually less than 40 cm.

Facial. Cleft lip with or without cleft palate and prominent premaxilla, hypertelorism, midfacial capillary hemangioma, thin naries, shallow orbits and prominent eyes with bluish sclerae, micrognathia. Malformed ears with hypoplastic lobules.

Hair. Sparse, may be silvery-blond in some survivors.

Limb. Hypomelia, varying from phocomelia to lesser degrees of limb reduction, often including absent or malformed thumb, radial aplasia, syndactyly, clinodactyly of fifth finger, and talipes deformity. Incomplete development of dermal ridges.

Genitalia. Cryptorchidism. Phallus may *appear* relatively large in relation to body size.

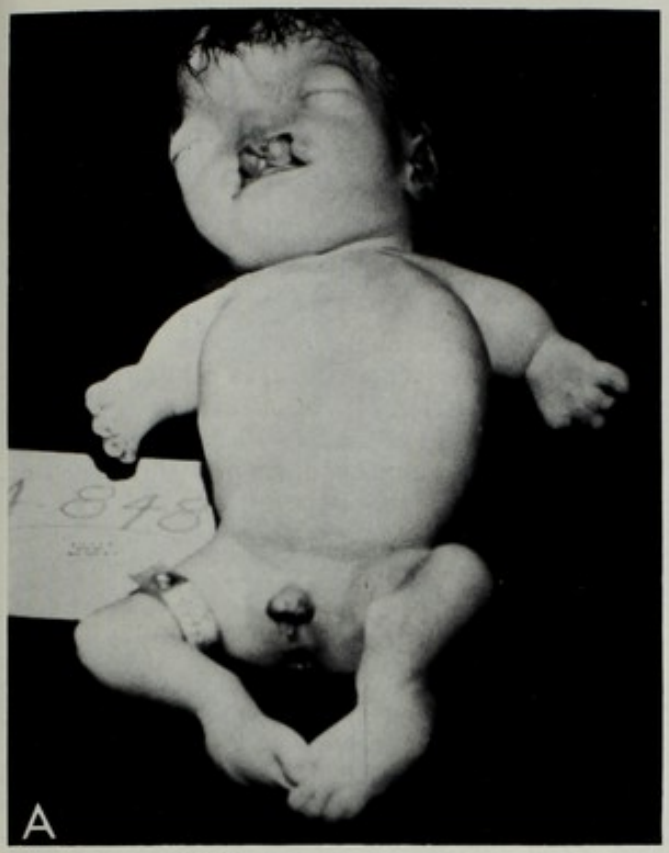
OCCASIONAL ABNORMALITIES. Frontal encephalocele, hydrocephalus, corneal clouding, cataract, short neck, cardiac anomaly (auricular septal defect), renal anomaly (polycystic, horseshoe), bicornuate uterus. Polyhydramnios.

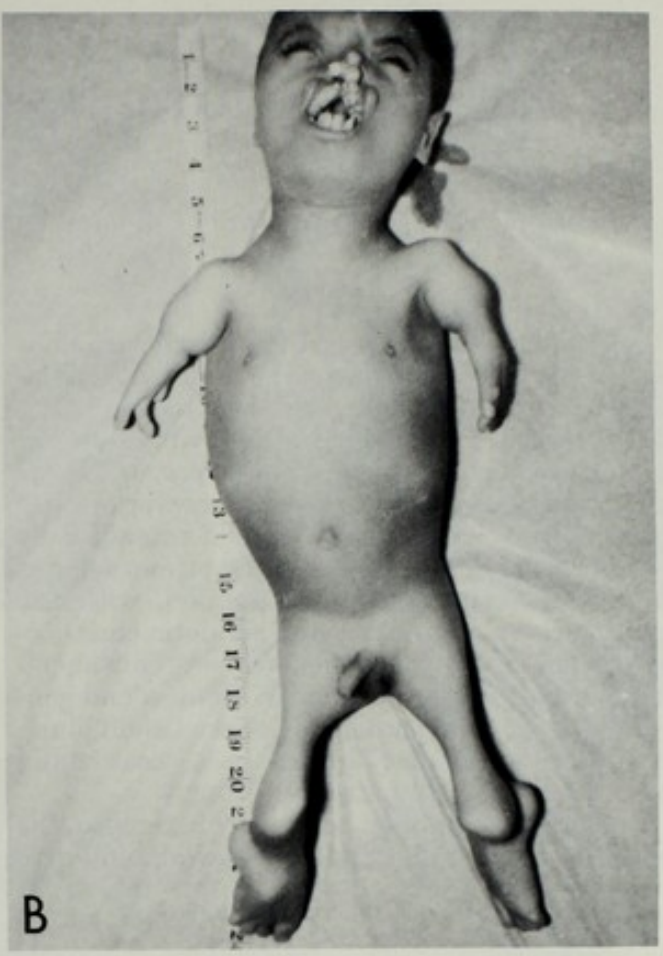
NATURAL HISTORY. Most cases have been stillborn or died in early infancy. The survivors have had marked growth deficiency and some have had severe mental deficiency as well. Judging from the published cases, the author would recommend a lack of early medical intervention toward survival in the cases having the more severe defect in midfacial and limb development.

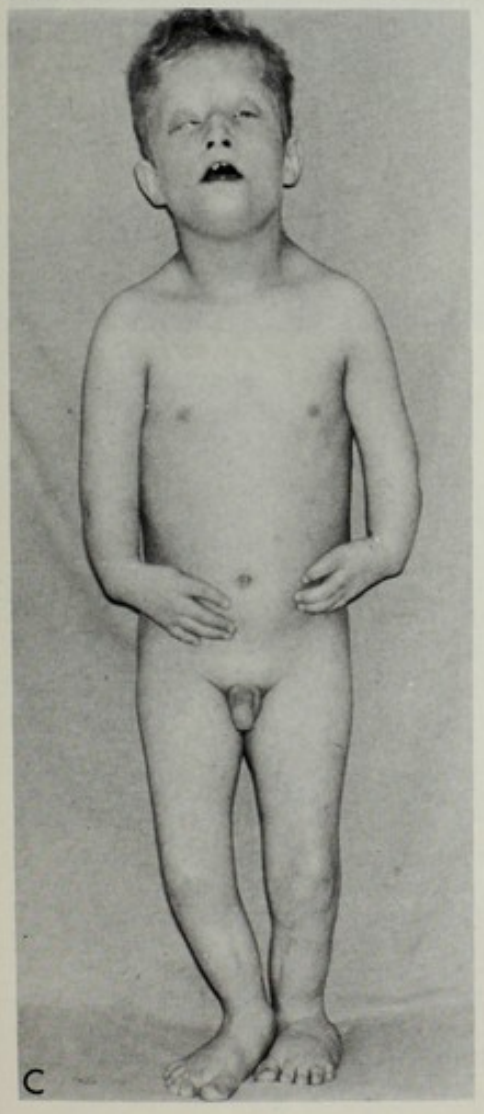
ETIOLOGY. Autosomal recessive.

REFERENCES

1. Roberts, J. B.: A child with double cleft of lip and palate, protrusion of the intermaxillary portion of the upper jaw and imperfect development of the bones of the four extremities. Ann. Surg., *70*:252, 1919.
2. Appelt, H., Gerken, H., and Lenz, W.: Tetraphokomelie mit Lippen-Kiefer-Gaumenspalte und Clitorishypertrophie – Ein Syndrom. Paediatr. Paedol., *2*:119, 1966.
3. Freeman, M. V. R., Williams, D. W., Schimke, N., Temtany, S. A., Vachier, E., and German, J.: The Roberts syndrome. Clin. Genet., *5*:1, 1974.
4. Herrmann, J., Feingold, M., Tuffli, D., and Opitz, J. M.: A familial dysmorphogenetic syndrome of limb deformities, characteristic facial appearance and associated anomalies: The pseudothalidomide or SC-syndrome. Birth Defects, *5*:81, 1969.
5. Hall, B. D., and Greenberg, M. H.: Hypomelia-hypotrichosis-facial hemangioma syndrome. Am. J. Dis. Child., *123*: 602, 1972.







A, Severely affected infant female at autopsy and, *B*, her severely growth and mentally deficient ten year old brother. (From Freeman, M. V., et al.: Clin. Genet., *5*:1, 1974.)

C, Eight year old severely mentally deficient boy with silvery-blond hair and a height age of three and one half years. (From S. Jurenka, St. Amant Wards, Winnipeg.)

D, Same patient as an infant and at eight years of age. Note capillary hemangioma on forehead in infancy and sparse scalp hair as a child. (From Hall, B. D., and Greenberg, M. H.: Am. J. Dis. Child., *123*:602, 1972.)



AMNIOTIC BAND ANOMALADS

Primary Defect—Early Rupture of Amnion with Formation of Amnion and/or Chorion Strands

Partial to complete ring-like constrictions may result in anomaly of the limbs. At times fibrous-appearing bands have been noted at the sites of constriction, sometimes having a broken strand connected to the amnion proper. These bands, when present, become necrotic after birth. Torpin has summarized and extended the evidence which indicates that the primary defect is an early rupture of the amnion, with the chorion remaining intact and amniotic bands occurring as a secondary phenomenon. This anomaly is usually a sporadic one in families and generally occurs in an otherwise normal individual. A surgical procedure, Z-plasty, may occasionally be indicated for a constrictive "ring."

Such strands can become adherent to the early developing face and/or calvarium and give rise to disruptive clefts, asymmetric encephaloceles, and gross distortion, as illustrated. The head may occasionally be attached to the placenta. Other less common defects noted in such patients are incomplete upper limb development, scoliosis, and gastroschisis.

REFERENCES

1. Torpin, R.: Fetal Malformations Caused by Amnion Rupture during Gestation. Springfield, Ill., Charles C Thomas, 1965.
2. Jones, K. L., Smith, D. W., Hall, B. D., Hall, J. G., et al.: A pattern of craniofacial and limb defects secondary to aberrant tissue bands. J. Pediatr., *84*:90, 1974.



Above, Asymmetric encephaloceles and disruption of facial morphogenesis presumed to be secondary to aberrant tissue bands. The same patients had limb anomalies secondary to bands. *A,* Note the notch in the upper lip. *B,* Note the striking asymmetry of the encephalocele. *C,* Note the disruptive tissue bands extending upward from the apices of the facial clefts.

Below, Variable limb anomalies secondary to aberrant bands. *A,* The arrow denotes the broken band which caused the pseudosyndactyly. *B,* Band constricting the ankle. *C* and *D,* Pseudosyndactyly, amputation, and disruption of toe morphogenesis.

(From Jones, Kol., et al.: J. Pediatr., *84*:90, 1974.)

POLAND ANOMALAD

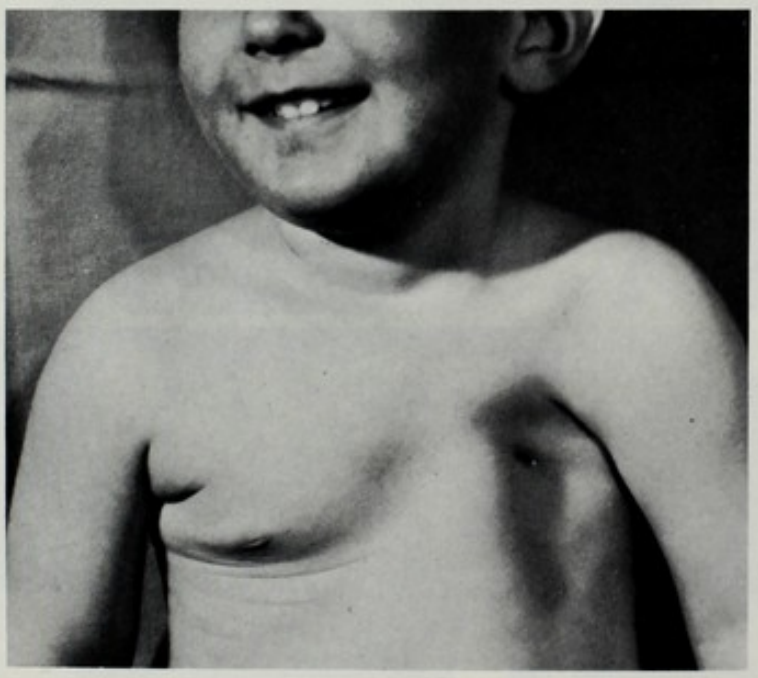
(Unilateral Defect of Pectoralis Muscle and Syndactyly of Hand)

Primary Defect—In Mesoderm, in Quadrant From Pectoral Area to Distal Limb

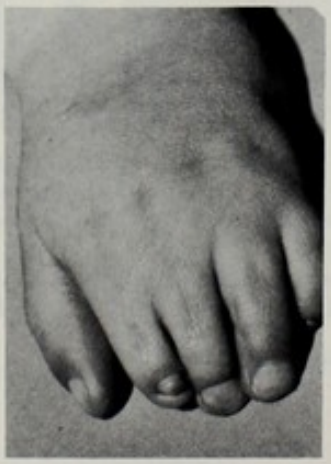
In 1841 Poland reported unilateral absence of the pectoralis minor and the sternal portion of the pectoralis major in an individual who also had cutaneous syndactyly of the hand on the same side. This unique pattern of malformation has subsequently been noted in numerous cases, and it has been estimated that 10 per cent of patients with syndactyly of the hand have the Poland anomalad. It is generally a unilateral sporadic occurrence in otherwise normal individuals. This pattern of malformation may include absence of the nipple and areola, rib defects, and hypoplasia of the hand or even the whole arm on the affected side.

REFERENCES

1. Poland, A.: Deficiency of the pectoral muscles. Guy's Hosp. Rep., *6*:191, 1841.
2. Clarkson, P.: Poland's syndactyly. Guy's Hosp. Rep., *111*:335, 1962.
3. Mace, J. W., Kaplan, J. M., Schanberger, J. E., and Gotlin, R. W.: Poland's syndrome. Clin. Pediatr. (Phila.), *11*:98, 1972.







Poland anomalad. The absence of the pectoralis minor and the sternal portion of the pectoralis major plus the ipsilateral syndactyly of the hand are the more usual features of this complex anomaly. The bony thoracic anomaly and the hypoplasia of the hand, as noted in this otherwise normal boy, are more severe expressions of this defect.

LIMB REDUCTION–ICHTHYOSIS SYNDROME

Unilateral Hypomelia and Skin Hypoplasia, Cardiac Defect

Falek, et al.[1] reported two female siblings with this unique unilateral pattern of malformation in 1968 and Shear[2] noted a comparable case.

ABNORMALITIES. Unilateral.

Growth. Mild prenatal growth deficiency.

Limbs. Moderate to severe hypomelia of limbs, +/− absent scapula and diminished ribs, webbed elbow and knee.

Skin. Thin, immature, slightly scaling skin on one side with sharp midline demarcation anteriorly.

Cardiac. Partial to complete absence of cardiac septum with valve defects, +/− truncus arteriosus.

Other. Absence of pectoralis major muscle.

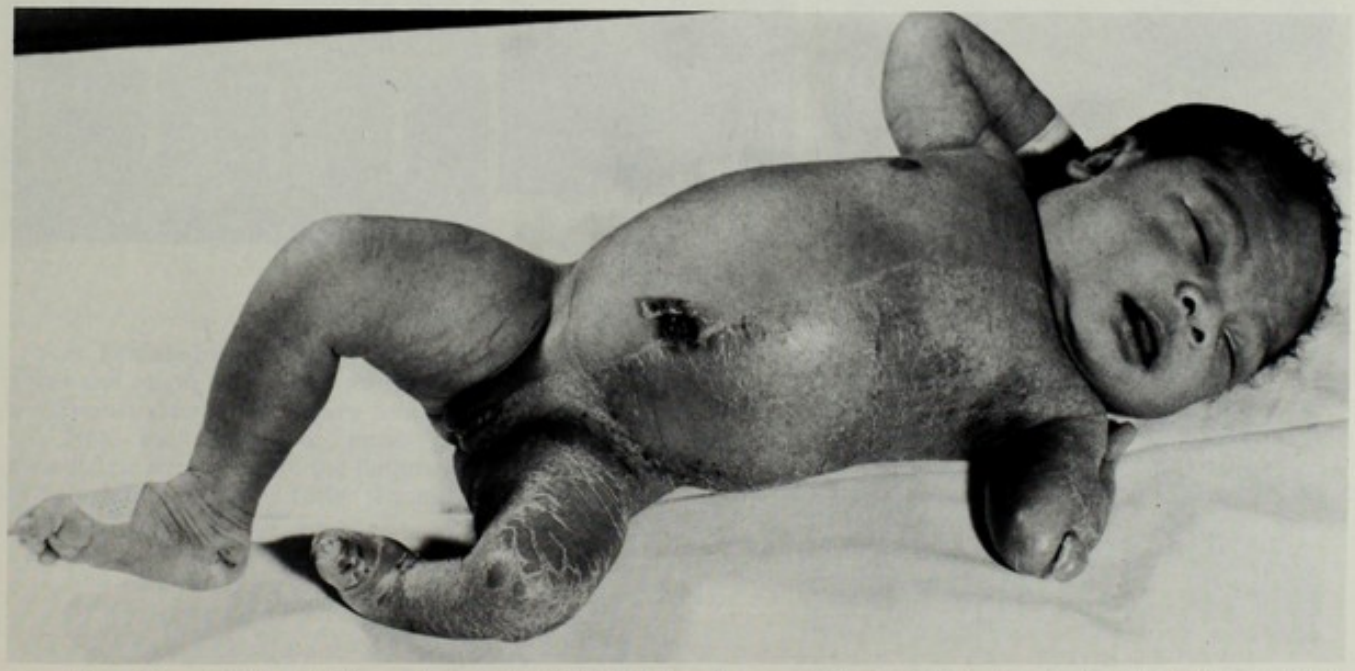
NATURAL HISTORY. Falek's patients died within several days after birth, apparently secondary to the cardiac defect. Shear's case survived and is mentally deficient.

ETIOLOGY. Unknown. The occurrence in siblings of normal parentage raises the question of autosomal recessive inheritance.

COMMENT. The striking left-sided asymmetry of expression in this disorder is unexplained but strongly suggests a very early asymmetric differential sensitivity toward the dysmorphogenic influence. The nature of the skeletal, skin, and heart defects indicates a very early problem in morphogenesis. If this defect were bilateral, it might well be an early prenatal lethal; hence it might only be seen as a unilateral occurrence.

REFERENCES

1. Falek, A., Heath, C. W., Ebbin, A. J., and McLean, W. R.: Unilateral limb and skin deformities with congenital heart disease in twin siblings. A lethal syndrome. J. Pediatr., *73*:910, 1968.
2. Carol Shear, M.D. Personal communication.



One of two affected siblings, both with left-sided involvement. (From Falek, A., et al.: J. Pediatr., *73*:910, 1968.)

FEMORAL HYPOPLASIA–UNUSUAL FACIES SYNDROME

Femoral Hypoplasia, Short Nose, Cleft Palate

Following single case reports in 1961 and 1965 by Franz and O'Rahilly[1] and by Kucera, Lenz, and Maier,[2] Daentl, et al.[3] recognized four additional patients and set forth this unique syndrome in 1974.

ABNORMALITIES. Six cases.[3]

Growth. Small stature, predominantly the result of short lower limbs.

Facial. Short nose with hypoplastic alae nasae, long philtrum and thin upper lip. Micrognathia, cleft palate. Upslanting palpebral fissures.

Limbs. Hypoplastic to absent femura and fibulae. Variable hypoplasia of humeri with restricted elbow movement, including synostosis. Club feet.

Pelvis. Hypoplastic acetabulae, constricted iliac base with vertical ischial axis, and large obturator foramina.

Spine. Lower spine abnormalities.

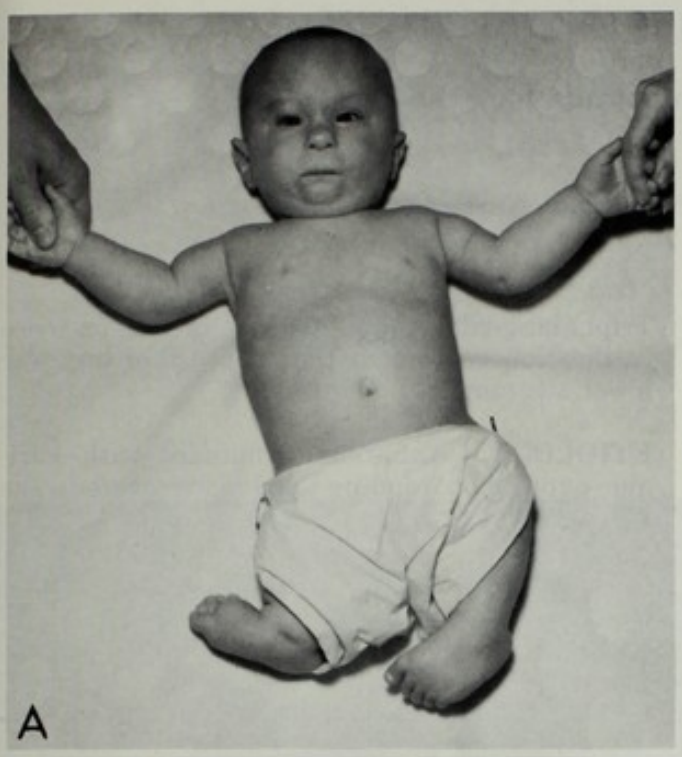
OCCASIONAL ABNORMALITIES. Astigmatism, esotropia, short third, fourth, and fifth metatarsals, inguinal hernia, cryptorchidism.

NATURAL HISTORY. Though there may be problems in speech development, the patients have been of normal intelligence. Most of them have been ambulatory.

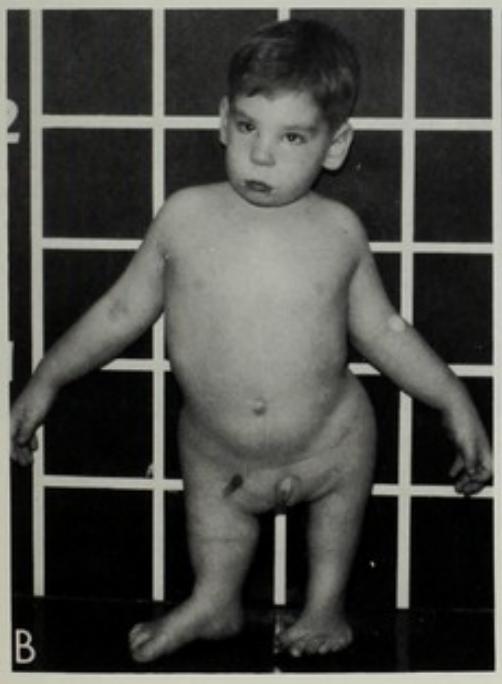
ETIOLOGY. Unknown. All cases have been sporadic.

REFERENCES

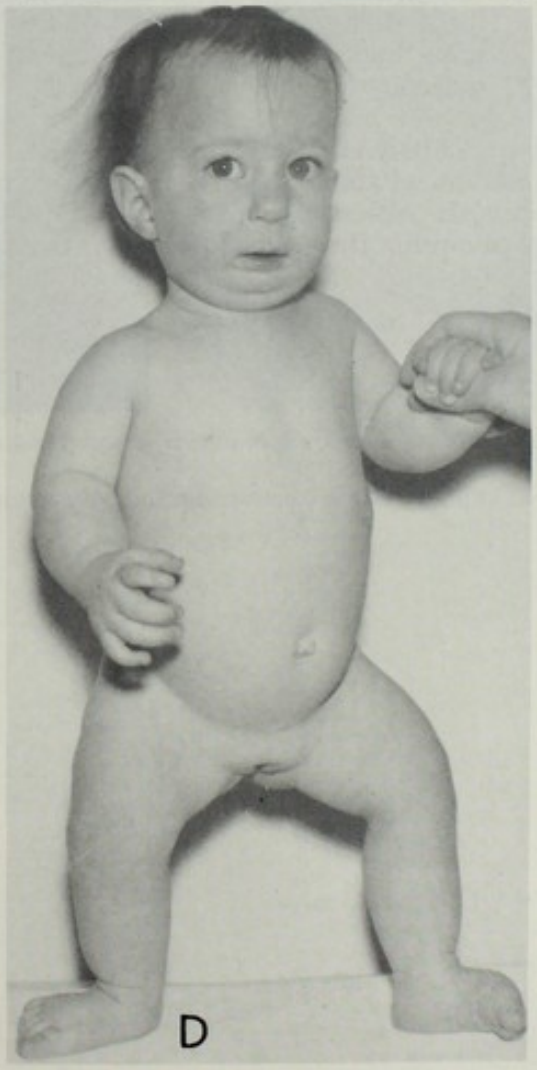
1. Franz, C. H., and O'Rahilly, R.: Congenital skeletal limb deficiencies. J. Bone Joint Surg. [Am.], *43*:1202, 1961.
2. Kucera, V. J., Lenz, W., and Maier, W.: Missbildungen der beine und der Kaudalen Wirbelsaule bei Kindern diabetischer Mutten. Dtsch. Med. Wochenschr., *90*:901, 1965.
3. Daentl, D. L., Smith, D. W., Scott, C. I., Hall, B. D., and Gooding, C. A.: Femoral hypoplasia-unusual facies syndrome. J. Pediatr., *86*:107, 1975.











A, Female infant. *B*, Five year old boy. *C* and *D*, Female infant and roentgenogram showing hypoplastic fibula and lag in mineralization of secondary centers at the knee.

Note the short nose, small mandible, variable and asymmetric hypoplasia of the femurs and humeri, and inability to extend the elbow fully. (From Daentl, D. L., et al.: J. Pediatr., *86*:107, 1975.)

HOLT-ORAM SYNDROME

(Cardiac-Limb Syndrome)

Upper Limb Defect, Cardiac Anomaly, Narrow Shoulders

This syndrome of skeletal and cardiovascular abnormality was first described by Holt and Oram in 1960.[1]

ABNORMALITIES

Skeletal. Hypoplasia and proximal placement of the thumb is the most common defect, but hypoplasia of the radius and even phocomelia may occur.

Hypoplasia of the clavicles with narrow shoulders.

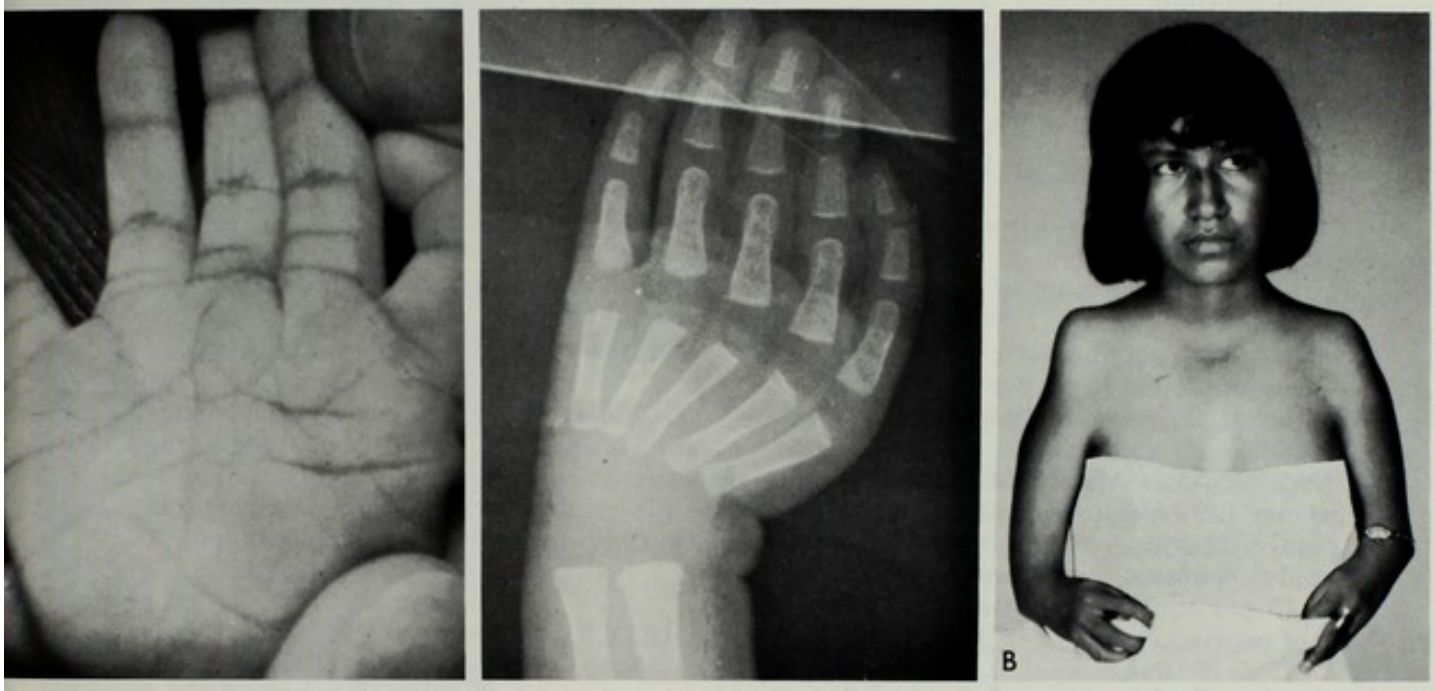
Cardiovascular. Auricular septal defect, sometimes with arrhythmia, and ventricular septal defect have been the most common defects, and about one third of the patients have had other types of congenital heart defects.

OCCASIONAL ABNORMALITIES. Hypertelorism. Patent ductus arteriosus, pulmonic stenosis. Absent pectoralis major muscle. Pectus excavatum, thoracic scoliosis. Small scapulae. Triphalangeal thumb. Absence of one or more ossification centers in the wrist. Skin tag over lower sternum.

ETIOLOGY. Autosomal dominant with variable expression, tending to be more severe in the female.

REFERENCES

1. Holt, M., and Oram, S.: Familial heart disease with skeletal malformations. Br. Heart J., *22*:236, 1960.
2. Lewis, K. B., Bruce, R. A., Baum, D., and Motulsky, A. G.: The upper limb-cardiovascular syndrome. An autosomal dominant genetic effect on embryogenesis. J.A.M.A., *193*:1080, 1965.
3. Kaufman, R. L., Rimoin, D. L., McAlister, W. H., and Hartmann, A. F.: Variable expression of the Holt-Oram syndrome. Am. J. Dis. Child., *127*:21, 1974.



A, Finger-like thumb (to right) in an infant with the Holt-Oram syndrome. (From M. Feingold, Tufts Medical School.)

B, Fifteen year old with auricular septal defect. Note severe forearm hypoplasia, absence of thumbs, and altered shoulder girdle.

FANCONI PANCYTOPENIA SYNDROME

Radial Hypoplasia, Hyperpigmentation, Pancytopenia

Since Fanconi's[1] original description of three affected siblings in 1927, over 160 cases have been reported.

ABNORMALITIES. Percentage of patients noted to have each defect.[2]

Small stature	56%
Small cranium	43%
Hypoplasia to aplasia of thumb	78%

Pancytopenia: because marrow failure has generally been an essential prerequisite to the diagnosis, it is difficult to know its true incidence; however, it is presumably a usual feature.

Splenic hypoplasia is a frequent autopsy finding.

Brownish pigmentation of skin is a frequent feature.

Small penis, small testes, and/or cryptorchidism are found in 44 per cent of males.

Enhanced chromosomal breakage.

OCCASIONAL ABNORMALITIES. Mental deficiency (20+ per cent), ptosis of eyelid, strabismus, nystagmus, microphthalmos, auricular anomaly, deafness, osteoporosis, aplasia of radius (15 per cent), duplication of thumb, broad base of proximal phalanges, hypoplasia to aplasia of first metacarpal, diminished carpal centers, syndactyly, dislocation of hip, congenital heart defect, hypospadias, and leukemia.

NATURAL HISTORY. The majority of patients are relatively small at birth. Respiratory infections may be a frequent problem. The uneven brownish pigmentation of the skin tends to increase with age, being most evident in the anogenital area, groin, axilla, and trunk. Development of bleeding, pallor and/or recurring infection usually appears between five and ten years of age, although pancytopenia may occur in infancy or as late as the third decade. There are nests of hematopoiesis in the generally hypoplastic marrow. Some erythrocytes are macrocytic, there is a high percentage of fetal hemoglobin, and the red cell life span is shortened. The leukopenia is predominantly granulocytopenia. Previously the survival following discovery of pancytopenia was seldom more than two years, although recently combined therapy with testosterone and hydrocortisone analogue has extended the survival period.

ETIOLOGY. Autosomal recessive. An occasional parent may have a malformation (one case), slight pancytopenia (one case), or neutropenia, and leukemia was found in an otherwise normal relative in four of 48 affected families[3]; all possible heterozygote manifestations.

COMMENT. A curious and consistent finding has been undue fragility of the chromosomes of in vitro cultured lymphocytes from patients with this syndrome,[4] a finding which may be related to the propensity to develop leukemia.

REFERENCES

1. Fanconi, G.: Die familiäre Panmyelopathie. Schweiz. Med. Wochenschr., *94*:1309, 1964.
2. Nilsson, L. R.: Chronic pancytopenia with multiple congenital abnormalities (Fanconi's anaemia). Acta Paediatr., *49*:518, 1960.
3. Garriga, S., and Crosby, W. H.: The incidence of leukemia in families of patients with hypoplasia of the marrow. Blood, *14*:1008, 1959.
4. Schmid, W. K., Scharer, K., Baumann, T., and Fanconi, G.: Chromosomenbruchigkeit bei der familiären Panmyelopathie (Typus Fanconi). Schweiz. Med. Wochenschr., *95*:1461, 1965.



+ Pigmentation (brown) of skin

+ Short stature

+ Small cranium

+ Mental retardation

+ Strabismus

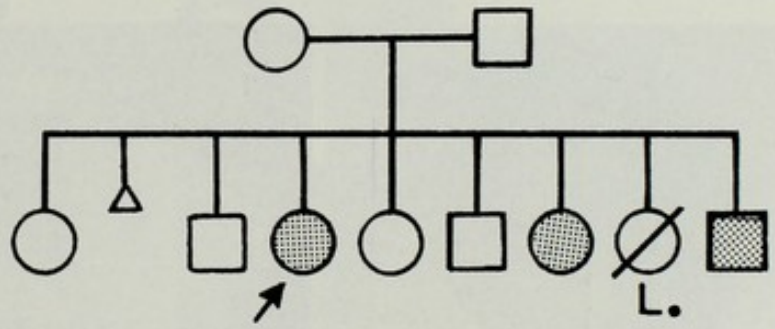
+ Abnormal ears

+ Abnormal thumbs

+ Renal anomaly

+ Hypoplasia of marrow, with time

Seven year old with a height age of three and one half years who has the anomalies listed above. The pedigree notes two affected siblings and one otherwise normal brother who died of leukemia during infancy. (From Smith, D. W.: J. Pediatr., *70*:479, 1967.)



RADIAL APLASIA–THROMBOCYTOPENIA SYNDROME

Gross, Groh, and Weippl[1] described this entity in siblings in 1956; subsequently over 20 cases have been reported.

ABNORMALITIES

Hematologic. Most severe in early infancy.

Thrombocytopenia with absence or hypoplasia of megakaryocytes (absent in 66 per cent, decreased in 12 per cent, inactive in 12 per cent).

"Leukemoid" granulocytosis in 62 per cent of cases, especially during bleeding episodes. Eosinophilia in 53 per cent.

Anemia, often out of proportion to apparent blood loss.

Absence or Hypoplasia of Radius. Usually bilateral; often with associated ulnar hypoplasia and defects of the hand, legs, and/or feet. However, the thumbs are present.

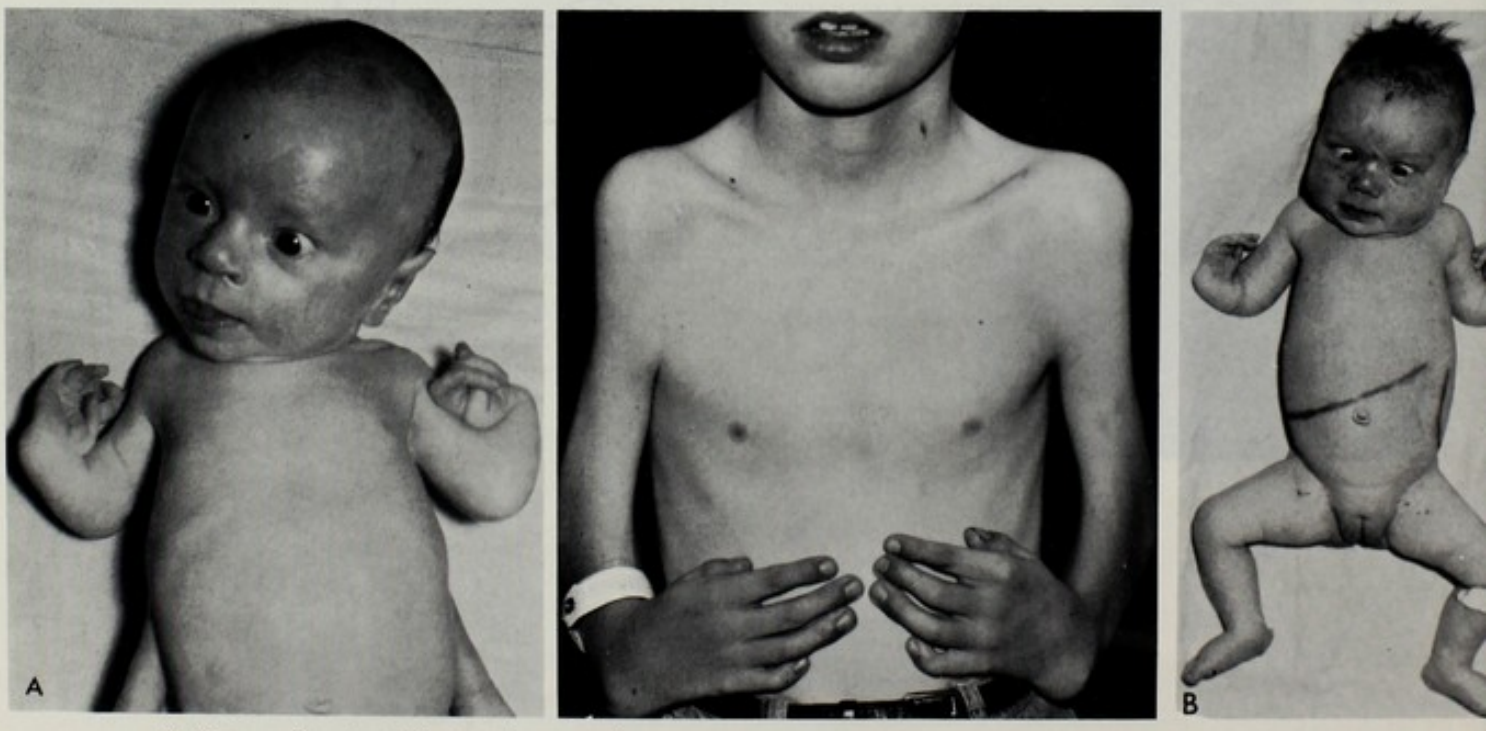
OCCASIONAL ABNORMALITIES. About 25 per cent have a congenital heart defect. Small stature, nevus flameus of forehead, genu varum, renal anomaly, and spina bifida, brachycephaly, strabismus, micrognathia, syndactyly, short humerus, hypoplastic shoulder girdle, dislocation of the hip, talipes foot deformity and Meckel's diverticulum. One patient developed leukemia, indicating that this unstable hematologic disorder may predispose toward development of leukemia.

NATURAL HISTORY. About 40 per cent of the patients have expired, usually as a result of hemorrhage during early infancy. With advancing age the severity of the hematological disorder usually becomes less profound, and therefore vigorous early management is indicated. Hydrocortisone analogue therapy, though it may lessen the likelihood of hemorrhage, has not had a consistently beneficial effect on the thrombocytopenia.

ETIOLOGY. Autosomal recessive. Of interest is the fact that an uncle of one patient died of leukemia.

REFERENCES

1. Gross, H., Groh, C., and Weippl, G.: Congenitale hypoplastische Thrombopenie mit Radialaplasie. Neue Osterr. Z. Kinderheilkhd., *1*:574, 1956.
2. Shaw, S., and Oliver, R. A. M.: Congenital hypoplastic thrombocytopenia with skeletal deformities in siblings. Blood, *14*:374, 1956.
3. Hunter, R.: Congenital megakaryocytic hypoplasia with radial aplasia. Personal communication.



A, Same patient as infant and young boy.

B, Young infant with serious bleeding and hepatosplenomegaly. Patient also had a cardiac defect. (Courtesy of J. M. Opitz, University of Wisconsin, and R. Hunter, University of Washington.)

AASE SYNDROME

Triphalangeal Thumb, Congenital Anemia

Aase and Smith[1] described this disorder in two male siblings in 1969. At least two additional cases have been recognized.[2, 3]

ABNORMALITIES. Based on four cases.[1-3]

Growth. Mild growth deficiency, about third percentile.

Hematopoietic. Hypoplastic anemia which tends to improve with age. Variable leukopenia.

Skeletal. Triphalangeal thumbs, mild radial hypoplasia, narrow shoulders, late closure of fontanels.

Other. Cardiac defect, especially ventricular septal defect. Variable hepatosplenomegaly.

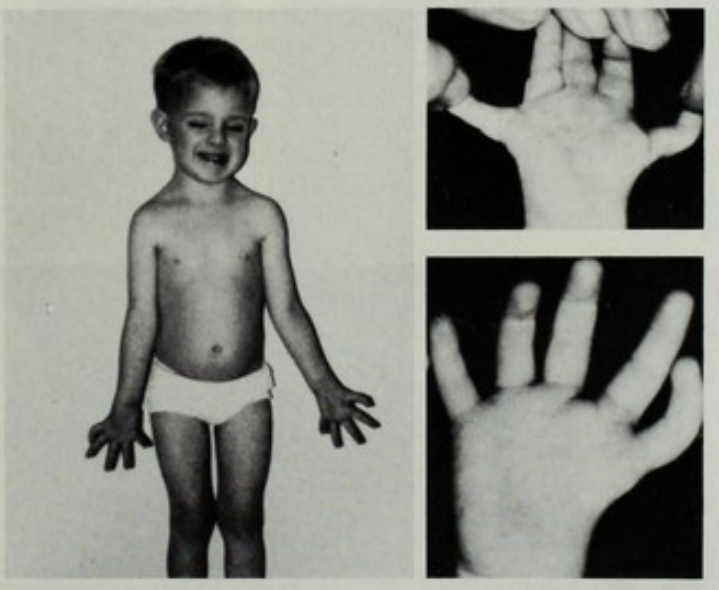
OCCASIONAL ABNORMALITIES. Found in one patient: cleft lip, cleft palate, retinopathy, web neck.

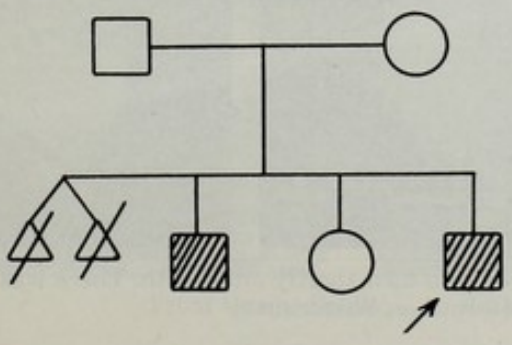
NATURAL HISTORY. The anemia, which has been responsive to prednisone therapy, tends to improve with age.

ETIOLOGY. Unknown. X-linked recessive inheritance is suggested by occurrence in males, two of whom are siblings; plus the unilateral triphalangeal thumb in the mother of one patient,[2] possibly a heterozygote expression.

REFERENCES

1. Aase, J. M., and Smith, D. W.: Congenital anemia and triphalangeal thumbs: A new syndrome. J. Pediatr., *74*:417, 1969.
2. Murphy, S., and Lubin, B.: Triphalangeal thumbs and congenital erythroid hypoplasia: Report of a case with unusual features. J. Pediatr., *81*:987, 1972.
3. Jones, B., and Thompson, H.: Triphalangeal thumbs associated with hypoplastic anemia. Pediatrics, *52*:609, 1973.





Affected boy who had been seriously anemic in infancy during which time the anemia responded to prednisone therapy. He is now mildly anemic without therapy. His brother, whose hand is also shown, is similarly affected. (From Aase, J. M., and Smith, D. W.: J. Pediatr., *74*:417, 1969.)

ACHONDROGENESIS SYNDROME

Low Nasal Bridge, Very Short Limbs, Incomplete Ossification of Lower Spine

This early lethal disorder was described in 1925 by Donath and Vogl[1] and termed achondrogenesis by Fraccaro in 1952.[2] More than 15 cases have been reported.

ABNORMALITIES

Growth. Extreme small stature, 25 to 38 cm.

Craniofacies. Cranium normal to large for gestational age. Low nasal bridge, micrognathia.

Limbs. Severe micromelia with wide humeral metaphyses and tendency toward metaphyseal bony "spurs" by x-ray. Disproportionately short first metacarpal and metatarsal. Lack of ossification of talus and calcaneus.

Trunk. Short with lack of mineralization of sternum and most caudal vertebrae. Short horizontal ribs.

Pelvis. Small with flat acetabulae.

Other. Often edematous, with polyhydramnios. Relatively large liver.

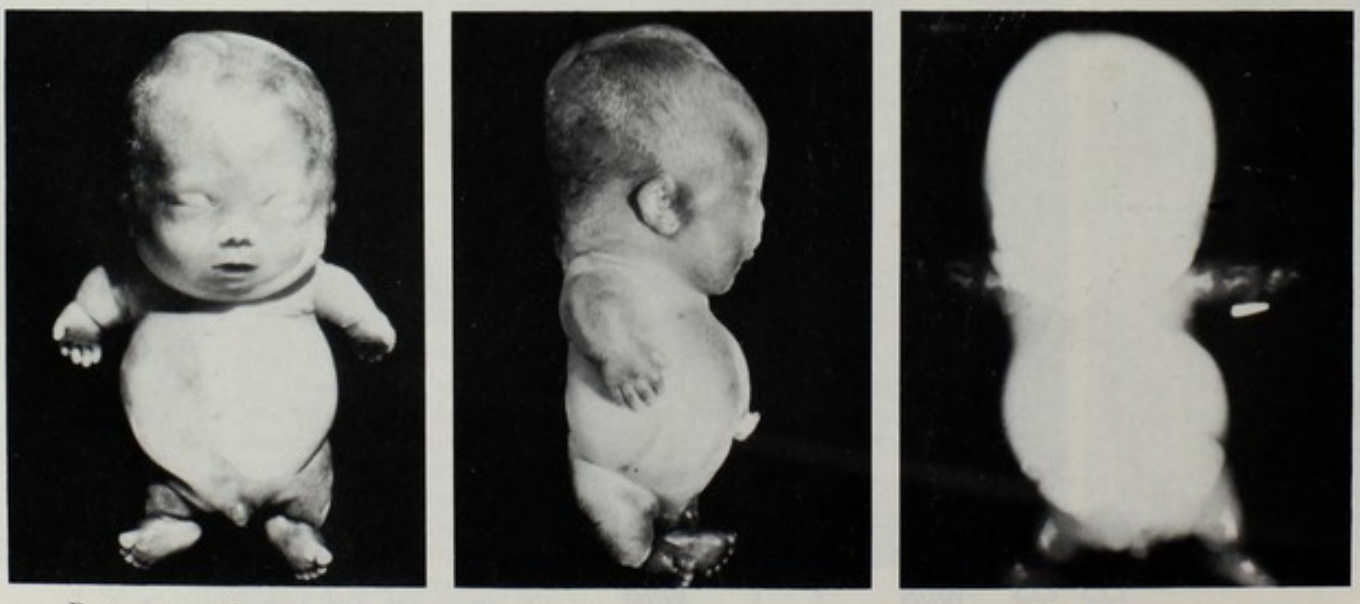
COMMENT AND NATURAL HISTORY. The defect in the development of cartilage and bone is severe. Epiphyseal cartilage is immature, disorganized, and lacking matrix between cells. Fibrous bands may be present between the epiphysis and metaphysis and the primary spongiosa is haphazardly arranged beneath the zone of provisional calcification. The ossification of the skeletal system has not progressed beyond the usual two- to three-month fetal level.

Developmental pathology beyond the skeletal system is implied by the frequent findings of polyhydramnios, appearance of hydrops, and the early lethality. Most cases are stillborn or die shortly after birth.

ETIOLOGY. Autosomal recessive inheritance is implied by the occurrence in two siblings of second cousin parentage.[4] The other cases have been sporadic. However, early gestational lethality may obscure the frequency of recurrence of this disorder.

REFERENCES

1. Donath, J., and Vogl, A.: Untersuchungen über den chondrodystrophischen Zwergwuchs. Wein. Arch. Intern. Med., *10*:1, 1925.
2. Fraccaro, M.: Contributo allo studio delle malattie del mesenchima osteopoietico. L'achondrogenesi. Folia Hered. Pathol. (Milano), *1*:190, 1952.
3. Maroteaux, P., and Lamy, M.: Le diagnostic des nanismes chondrodystrophiques chez les nouveau-nés. Arch. Fr. Pediatr., *25*:241, 1968.
4. Salding, R. M.: Lethal short-limbed dwarfism: Achondrogenesis and thanatophoric dwarfism. Am. J. Roentgenol. Radium Ther. Nucl. Med., *112*:185, 1971.



Postmortem photos and roentgenograph of baby who died shortly after birth. There was a lack of ossification of the lower spine. (Courtesy of S. R. Mallin, Milwaukee, Wisconsin.)

GREBE SYNDROME

(Achondrogenesis Syndrome, Type II)

Marked Distal Limb Reduction, Polydactyly, Normal Facies

Grebe[1] described this disorder in 1952, Quelce-Salgado reported 47 cases in five kindred in an inbred Brazilian population,[2] and Scott[3] recently summarized the findings.

ABNORMALITIES[1-3]

Growth. Small stature due to limb deficiency.

Limbs. Reduction, most striking distally with very short digits. Fingers resemble toes. Missing or hypoplastic bones. Legs shorter than arms. Valgus position of feet. Obese limbs.

NATURAL HISTORY. Many of the patients have been stillborn or died in infancy. Survivors are said to be of normal intelligence.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Grebe, H.: Die Achondrogenesis. Ein einfach rezessives Erbmerkmal. Folia Hered. Pathol. (Milano), *2*:23, 1952.
2. Quelce-Salgado, A.: A new type of dwarfism with various bone aplasias and hypoplasia of the extremities. Acta Genet., *14*:63, 1964.
3. Scott, C. I.: Skeletal dysplasias. Birth Defects, *5*(3): 14, 1969.



(From Quelco-Salgado, A.: Acta Genet., *14*:63, 1964.)

THANATOPHORIC DWARFISM SYNDROME

Short Limbs, Flat Vertebrae, Large Cranium with Low Nasal Bridge

Maroteaux, et al.[1] set forth this disorder in 1967 and utilized the Greek term thanatophoric (death-bringing) to emphasize that such patients usually die shortly after birth. In the past this disorder was often misdiagnosed as achondroplasia. For example, Harris and Patton[2] considered 10 of the 17 cases diagnosed as achondroplasia among 64,000 births at St. Mary's Hospital in Manchester to be instances of thanatophoric dwarfism, an incidence of about one in 6400.

ABNORMALITIES

Performance. Hypotonia.

Growth. Severe growth deficiency; 36 to 46 cm, average 40 cm.

Craniofacial. Large cranium and fontanel; 36 to 47 cm, average 37 cm. Small foramen magnum and short base of skull with full forehead, low nasal bridge, and small facies.

Limbs. Short with small sausage-like fingers, bowed long bones with cupped spur-like irregular flaring of metaphyses, and lack of ossification in secondary centers at knee. Disorganized chondrocytes and bony trabeculae, especially in central epiphyseal-metaphyseal region.

Thorax. Narrow with short ribs.

Spine. Short flattened vertebrae with relatively wide intervertebral disc space. Lack of caudal widening of spinal canal.

Scapulae. Small and squarish.

Pelvis. Squarish, short in height, with small sciatic notch and medial spurs.

ABNORMALITIES OF UNCERTAIN INCIDENCE

Brain anomalies including microgyria, absent corpus callosum, and faulty organization, especially in temporal lobe and cerebellum.[4, 5]

Extramedullary hematopoiesis.

OCCASIONAL ABNORMALITIES. Hydrocephalus, patent ductus arteriosus, auricular septal defect, horseshoe kidney, hydronephrosis, imperforate anus, "cloverleaf" skull, radio-ulnar synostosis.

NATURAL HISTORY. Feeble fetal activity and/or polyhydramnios are frequent in this disorder. Should such features lead to a prenatal x-ray diagnosis, early induction of delivery has been recommended[6] in order to avoid serious delivery problems at a later date (related to large head and/or breech presentation).

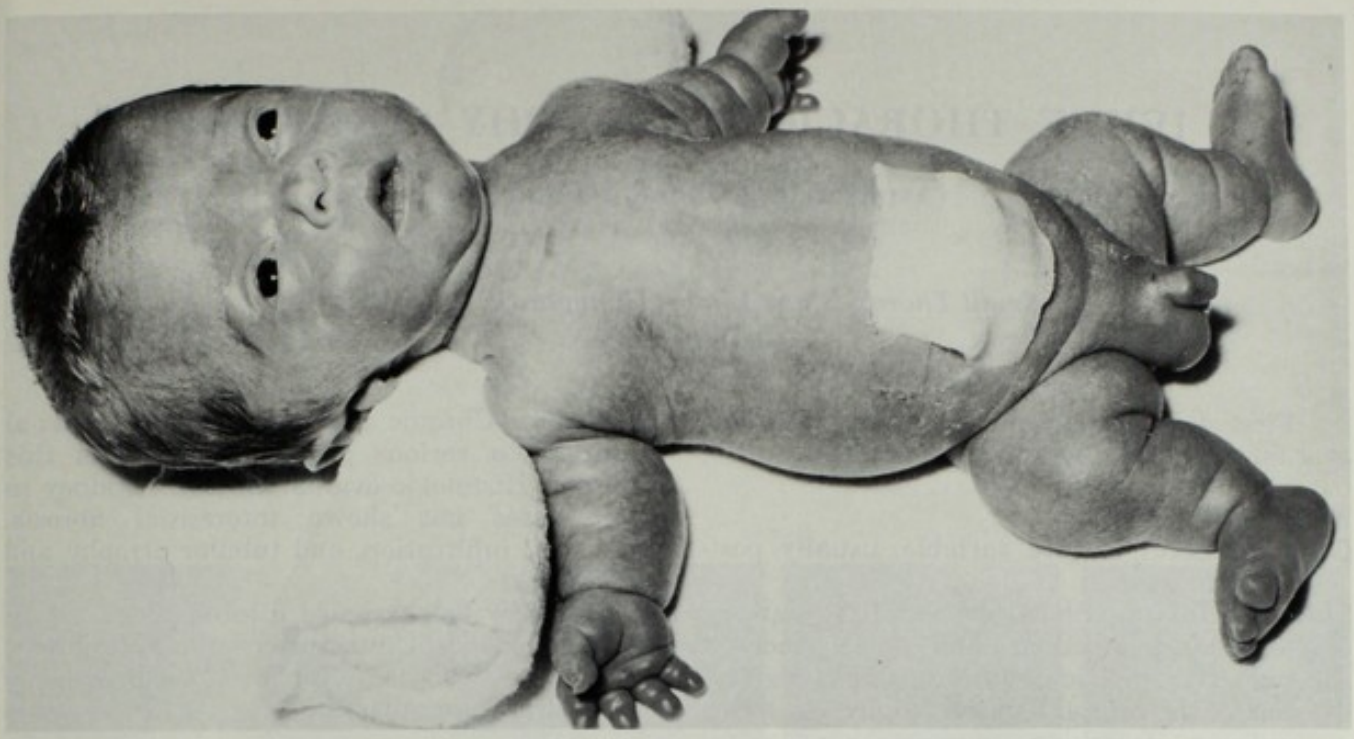
These patients usually die shortly after birth, at least partially due to the small thoracic cage and respiratory insufficiency. The longest survival was 25 days. The author recommends no medical intervention toward survival for patients with this disorder.

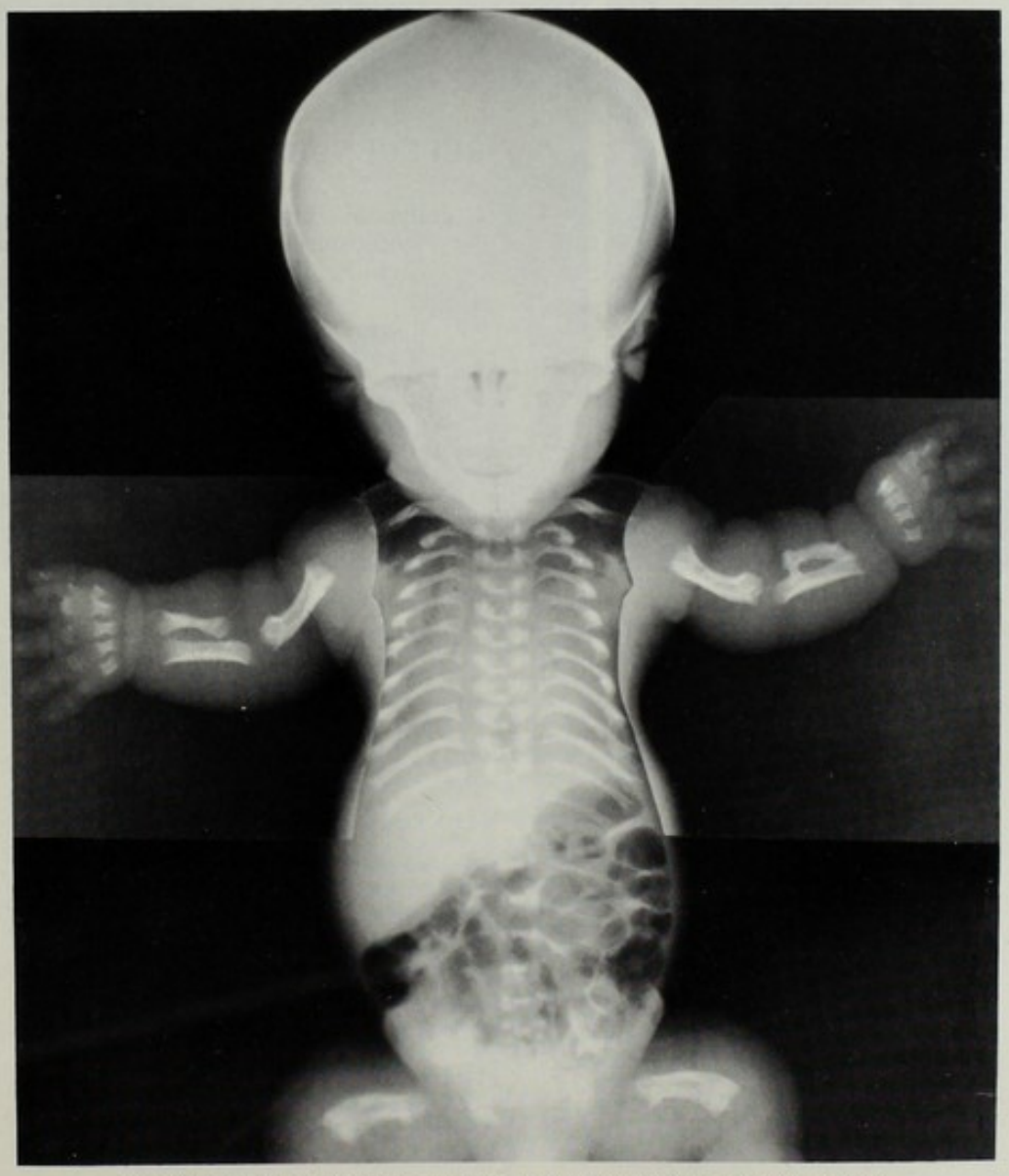
ETIOLOGY. Unknown. Most cases have been sporadic, with about a 2:1 ratio of affected males to females. Autosomal recessive inheritance has been implicated in at least one instance of two affected siblings born of consanguinous parentage.[7] The general empiric recurrence risk is about one in 50.

COMMENT. There is a striking resemblance between this disorder and an autosomal recessive early lethal type of achondroplasia in the rabbit.[8] Studies in the rabbit homozygote have demonstrated a mitochondrial defect in energy generation.

REFERENCES

1. Maroteaux, P., Lamy, M., and Robert, J. M.: Le nanisme thanatophere. Presse Med., *75*:2519, 1967.
2. Harris, R., and Patton, J. R.: Achondroplasia and thanatophoric dwarfism in the newborn. Clin. Genet., *2*:61, 1971.
3. Giedion, A.: Thanatophoric dwarfism. Helv. Paediatr. Acta, *23*:175, 1968.
4. Huguenin, M., Godard, C., Ferrier, P. E., and Bamatter, F.: Two different mutations within the same sibship: Thanatophoric dwarfism and Ullrich-Feichtiger syndrome. Helv. Paediatr. Acta, *24*:239, 1969.
5. Goutières, F., Aicardi, J., and Farkas-Bargeton, E.: Une malformation cérébrale particulière associée au nanisme thanatophore. Presse Med., *79*:960, 1971.
6. Thompson, B. H., and Parmley, T. H.: Obstetric features of thanatophoric dwarfism. Am. J. Obstet. Gynecol., *109*:396, 1971.
7. Chemke, J., Graff, G., and Lancet, M.: Familial thanatophoric dwarfism. Lancet, *1*:1358, 1971.
8. Shepard, T. H., Fry, L. R., and Moffett, B. C., Jr.: Microscopic studies of achondroplastic rabbit cartilage. Teratology, *2*:13, 1969.





Newborn. (From Giedion, A.: Helv. Paediatr. Acta, *23*:175, 1968.)

JEUNE THORACIC DYSTROPHY SYNDROME

(Asphyxiating Thoracic Dystrophy)

Small Thorax, Short Limbs, Hypoplastic Iliac Wings

First described by Jeune, et al.[1] in 1955, over 50 cases have now been reported.

ABNORMALITIES

Growth. Short stature variable, usually postnatal in onset.

Skeletal. Infancy: Short ribs with irregular costochondral junctions and small thoracic cage. Hypoplastic iliac wings. Early ossification of the capital femoral epiphysis.

Childhood: Irregular epiphyses and metaphyses with relatively short limbs. Ulnae and fibulae relatively short. Cone-shaped epiphyses and early fusion between epiphyses and metaphyses of distal and middle phalanges.

OCCASIONAL ABNORMALITIES. Polydactyly, usually of hands and feet, notching of distal end of metacarpal and metatarsal bones, lacunar skull, chronic nephritis.

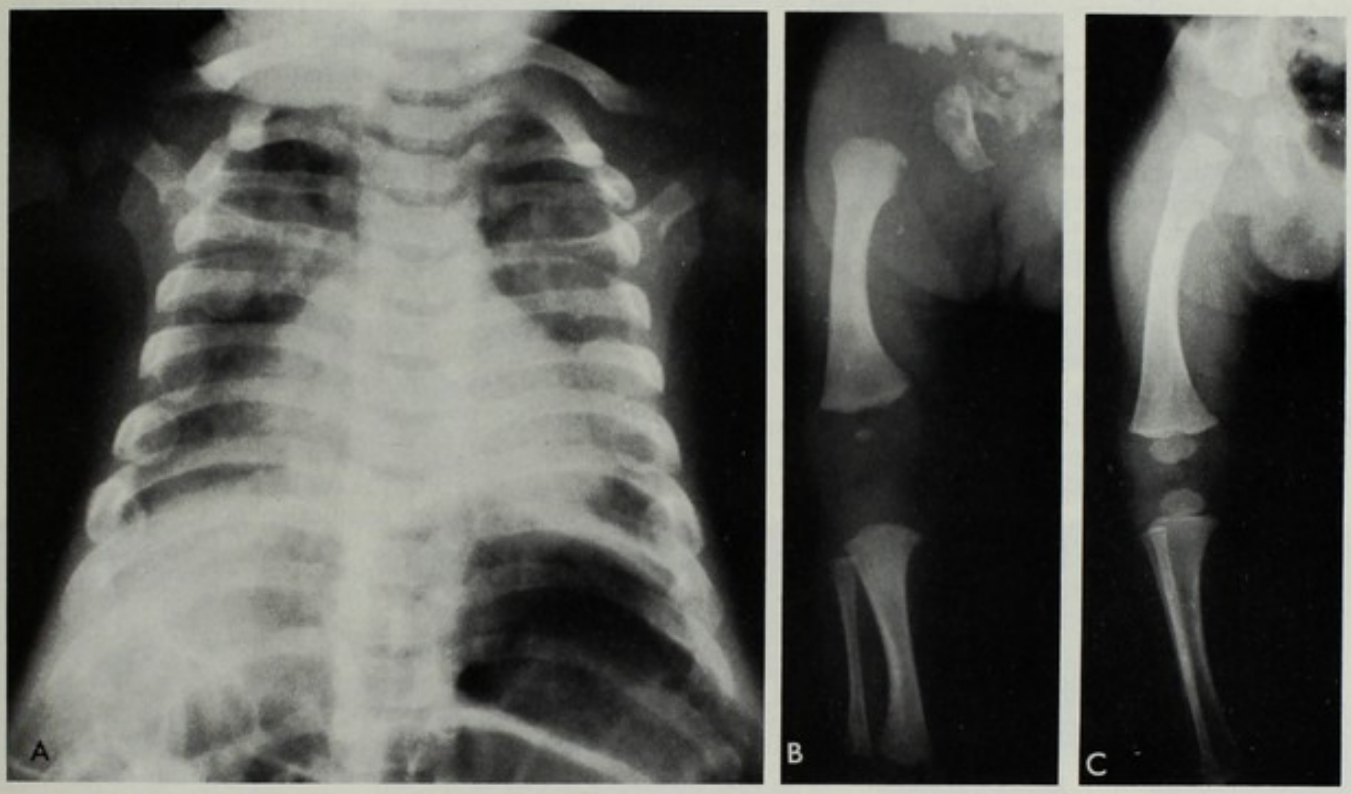
NATURAL HISTORY. Early death, usually the consequence of asphyxia with or without pneumonia in about one half of the cases. Those who survive usually have progressive improvement in the relative growth of the thoracic cage and may have only mild to moderate shortness of stature. Chronic nephritis leading to renal failure is a serious potential feature of this disorder. Histologic evaluation of the kidney in three cases has shown interstitial fibrosis, round-cell infiltration, and tubular atrophy and dilatation.

Autopsy has revealed disordered growth at the costochondral juncture with hyperplastic proliferating cartilage and poor progression of enchondral mineralization.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Jeune, M., Beraud, C., and Carron, R.: Dystrophie thoracique asphyxiante de caractère familial. Arch. Fr. Pediatr., *12*:886, 1955.
2. Pirnar, T., and Neuhauser, E. B. D.: Asphyxiating thoracic dystrophy of the newborn. Am. J. Roentgenol. Radium Ther. Nucl. Med., *98*:358, 1966.
3. Langer, L. O.: Thoracic-Pelvic-Phalangeal dystrophy. Radiology, *91*:447, 1968.
4. Herdman, R. C., and Langer, L. O.: The thoracic asphyxiant dystrophy and renal disease. Am. J. Dis. Child., *116*:192, 1968.



A, Four month old. Note short ribs, high position of clavicles.

B and *C*, Right lower extremity at one month and ten months of age showing improvement in long bones and pelvis, though fibula remains relatively short.

(From Hanissian, A. S., et al.: J. Pediatr., *71*:855, 1967.)

CAMPTOMELIC DWARFISM SYNDROME

Bowed Tibiae, Hypoplastic Scapulae, Flat Facies

Though reports of this condition appeared in the 1950's by Bound, et al.[1] and Bain and Barrett,[2] it was not until the 1970's that the syndrome became more broadly recognized by Spranger, et al.[3] and Maroteaux, et al.,[4] who utilized the term "campomelique," meaning bent limb, to epitomize the disorder.

ABNORMALITIES[1-6]

Growth. Prenatal onset growth deficiency with retarded osseous maturation. Birth length 35 to 49 cm. Diminished subcutaneous fat.

Central Nervous System. Tendency toward large brain with gross cellular disorganization, most evident in cerebral cortex, thalamus, and caudate nucleus.

Facies. Flat-appearing small face with low nasal bridge and micrognathia with antigonial notching.

Limbs. Anterior bowing of tibiae with cortical thickening of concave border and skin dimpling over convex area, short fibulae, mild bowing of femurs, and equinovarus.

Other Skeletal. Short and somewhat flat vertebrae. Hypoplastic scapulae, small thoracic cage with thin short clavicles, kyphoscoliosis, and small iliac wings with relatively wide pelvic outlet.

Tracheobronchial. Incomplete cartilaginous development with tracheobronchiomalacia.

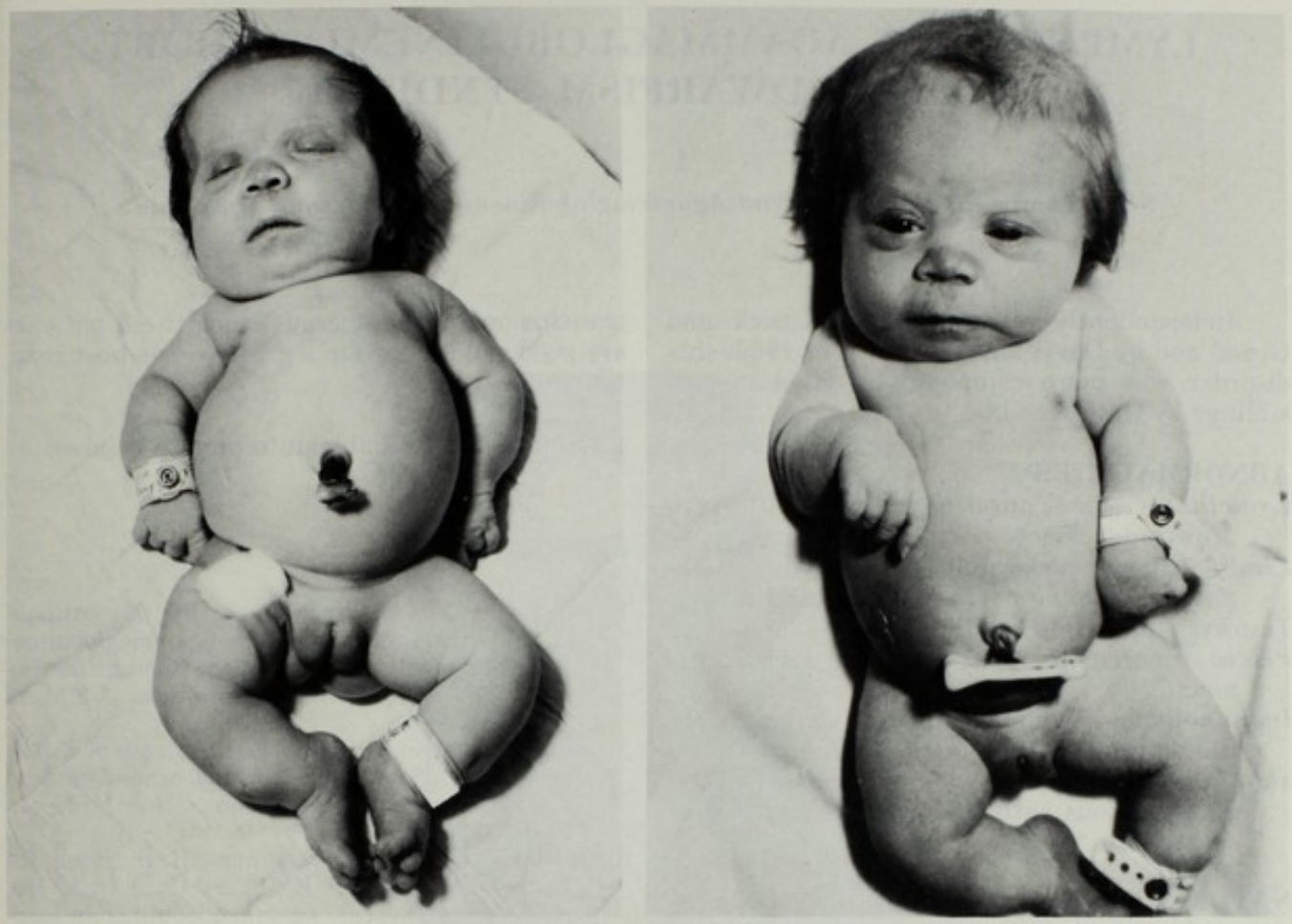
OCCASIONAL OR UNCERTAIN FREQUENCY. Polyhydramnios, macrocephaly, cleft soft palate, low-set ears, hypertelorism, platybasia, cervical vertebral anomalies, scoliosis, rib anomalies, short proximal phalanges, short radii, radioulnar dislocation, short proximal phalanges of big toes, patent ductus arteriosus.

NATURAL HISTORY. The great majority of patients die in the neonatal period from respiratory insufficiency and those surviving into early infancy have feeding problems, failure to thrive, and evidences of serious central nervous system deficiency, including apneic spells. Considering the natural history and the serious defect in brain organization, a lack of medical intervention should be considered when this clinical diagnosis is made.

ETIOLOGY. Unknown. Autosomal dominant inheritance is implied by an affected mother having had three affected offspring. The other cases have been sporadic, from unaffected parents.

REFERENCES

1. Bound, J. P., Finlay, H. V. L., and Rose, F. C.: Congenital anterior angulation of the tibia. Arch. Dis. Child., *27*:179, 1952.
2. Bain, A. D., and Barrett, H. S.: Congenital bowing of the long bones: Report of a case. Arch. Dis. Child., *34*:516, 1959.
3. Spranger, J., Langer, L. O., and Maroteaux, P.: Increasing frequency of a syndrome of multiple osseous defects? Lancet, *2*:716, 1970.
4. Maroteaux, P., Spranger, J., Opitz, J. M., Kucera, J., Lowry, R. B., Schimke, R. N., and Kagan, S. M.: Le syndrome campomélique. Presse Med., *79*:1157, 1971.
5. Hoefnagel, D., Wurster, D., Carey, D., Harris, G. J., and Pilliod, J.: Camptomelic dwarfism. Lancet, *1*:1068, 1972.
6. Schmickel, R. D., Heidelberger, K. P., and Poznanski, A. K.: The campomelique syndrome. J. Pediatr., *82*:299, 1973.



Two newborn babies showing low nasal bridge, micrognathia, small thorax, aberrant hand positioning, and bowed tibiae with dimples at the maximal point of bowing. Roentgenogram shows the slim, poorly developed bones and osseous immaturity (knee and foot). (Courtesy of D. Hoefnagel, Dartmouth Medical School, and of D. Hoefnagel, et al.: Lancet, *1*:1068, 1972.)

LYMPHOPENIC AGAMMAGLOBULINEMIA – SHORT-LIMBED DWARFISM SYNDROME

Short Limbs, Lymphopenia and Agammaglobulinemia, Ectodermal Dysplasia

Independently reported by McKusick and Gross[1] and by Davis and Williams[2] in 1966, this disorder was more completely studied in two siblings by Gatti, et al.[3]

ABNORMALITIES[1-3]

Growth. Prenatal onset of moderate to severe growth deficiency.

Limbs. Short, moderately curved, with metaphyseal cupping noted in radius and ulna.

Thorax. Relatively small.

Pelvis. Short with relatively large sacrosciatic notch.

Immunologic. Lymphopenia and agammaglobulinemia with hypoplastic thymus.

Skin. Redundant skin which tends to become erythematous with dyskeratosis and loss of sparse hair.

NATURAL HISTORY. Failure to thrive with repeated infectious episodes and diarrhea usually results in early death during infancy. Bone marrow failure may occur, for which fresh transfusions are dangerous since these patients are good candidates for a graft versus host reaction.

ETIOLOGY. Probable autosomal recessive.

REFERENCES

1. McKusick, V. A., and Gross, H. E.: Ataxia-telangiectasia and Swiss-type agammaglobulinemia. Two genetic disorders of the immune mechanism in related Amish sibships. J.A.M.A., *195*:739, 1966.
2. Davis, J. A., and Williams, E. D.: A case of Swiss-type agammaglobulinaemia and achondroplasia. Clinicopathological conference. Br. Med. J., *2*:1371, 1966.
3. Gatti, R. A., Platt, N., Pomerance, H. H., Hong, R., Langer, L. O., Kay, H. E. M., and Good, R. A.: Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of short-limbed dwarfism and ectodermal dysplasia. J. Pediatr., *75*:675, 1969.



Affected infant. (From Gatti, R. A., et al.: J. Pediatr., *75*:675, 1969.)

ACHONDROPLASIA SYNDROME

Short Limbs, Low Nasal Bridge, Caudal Narrowing of Spinal Canal

The most common chondrodysplasia, true achondroplasia occurs with a frequency of about one in 10,000.

ABNORMALITIES

Growth. Small stature. Mean adult height in males is 131 ± 5.6 cm, and in females is 124 ± 5.9 cm.

Craniofacial. Megacephaly, small foramen magnum.

Short cranial base with early spheno-occipital closure.

Low nasal bridge with prominent forehead.

Mild midfacial hypoplasia with narrow nasal passages.

Skeletal. Small cuboid shaped vertebral bodies with short pedicles and progressive narrowing of lumbar interpedicular distance.

Lumbar lordosis, mild thoracolumbar kyphosis with anterior beaking of first and/or second lumbar vertebrae.

Small iliac wings with narrow greater sciatic notch.

Short tubular bones, especially humeri; metaphyseal flare with ball and socket arrangement of epiphysis to metaphysis.

Short trident hand, fingers being similar in length, with short proximal and midphalanges.

Short femoral neck, incomplete extension of elbow.

Other. Mild hypotonia. Early motor progress is often slow, although eventual intelligence is usually normal. Relative glucose intolerance evident with an oral glucose tolerance test.

OCCASIONAL COMPLICATIONS. Hydrocephalus secondary to a narrow foramen magnum may occur. Spinal cord and/or root compression may occur as a consequence of kyphosis, stenosis of the spinal canal, or disc lesions. About 46 per cent of patients have spinal complications and therefore a cautious orthopedic-neurologic follow-up is merited.

NATURAL HISTORY. The physician should be alert to detect any neurological complications due to bony or disc compression. Osteoarthritis is not a usual feature in the adult. Osteotomies for severe bowlegs are usually deferred until full growth has occurred.

ETIOLOGY. Autosomal dominant, about 90 per cent of the cases representing a fresh mutation. Older paternal age has been a contributing factor in the fresh achondroplasia mutations, which have been estimated to occur once per 12,000 births.[5]

COMMENT. Histologic evaluation at the epiphyseal line discloses shorter cartilage columns which lack the usual linear arrangement, and some cartilage cells appear to be undergoing a mucinoid degeneration.

REFERENCES

1. Caffey, J.: Pediatric X-Ray Diagnosis. 5th ed. Chicago, Year Book Medical Publishers, 1967, p. 819.
2. Maroteaux, P., and Lamy, M.: Achondroplasia in man and animals. Clin. Orthop., *33*:91, 1964.
3. Shepard, T. H., and Graham, B.: The congenitally malformed. XIII. Achondroplastic dwarfism; diagnosis and management. Northwest Med., *66*:451, 1967.
4. Cohen, M. E., Rosenthal, A. D., and Matson, D. D.: Neurological abnormalities in achondroplastic children. J. Pediatr., *71*:367, 1967.
5. Mörch, E. T.: Achondroplasia is always hereditary and is inherited dominantly. J. Hered., *31*:439, 1940.
6. Nelson, M. A.: Spinal stenosis in achondroplasia. Proc. R. Soc. Med., *65*:1028, 1972.
7. Collipp, P. J., et al.: Abnormal glucose tolerance in children with achondroplasia. Am. J. Dis. Child., *124*:682, 1972.



A, One year old with height age of four months. (From Smith, D. W.: J. Pediatr., *70*:504, 1967.)
B, Four year old with height age of 20 months.
C, Short "trident" hand with short metacarpals and phalanges.
D, Caudal narrowing of spinal canal (pedicles marked) with short pedicles *(upper right)*.

HYPOCHONDROPLASIA SYNDROME

Short Limbs, Caudal Narrowing of Spine, Near-Normal Craniofacies

Though the features of this disorder were described by Ravenna in 1913[1] and its designation as hypochondroplasia and mode of inheritance set forth in 1924,[2] the majority of cases have been misdiagnosed as achondroplasia until recent times. Hypochondroplasia has an incidence about one twelfth that of achondroplasia and can be distinguished from it by the relative lack of craniofacial involvement and milder features in hands and spine in hypochondroplasia.[3, 4]

ABNORMALITIES[3, 4]

Growth. Small stature, usually of prenatal onset. Mean birth length 47.7 cm and birth weight 2.9 kg.

Limbs. Relatively short with mild V-shaped metaphyseal indentation and flaring, prominent bony sites of muscle attachment, bowing of lower limbs, stubby hands and feet with or without relatively long distal ulnae and fibulae. Mild elbow limitation in extension and supination.

Spine. Bony spinal canal narrowing caudally, with or without lumbar lordosis.

Pelvis. Hypoplasia of the ilia with small greater sciatic notches.

OCCASIONAL ABNORMALITIES. Mental deficiency, brachycephaly with short base of skull, and mild frontal bossing.

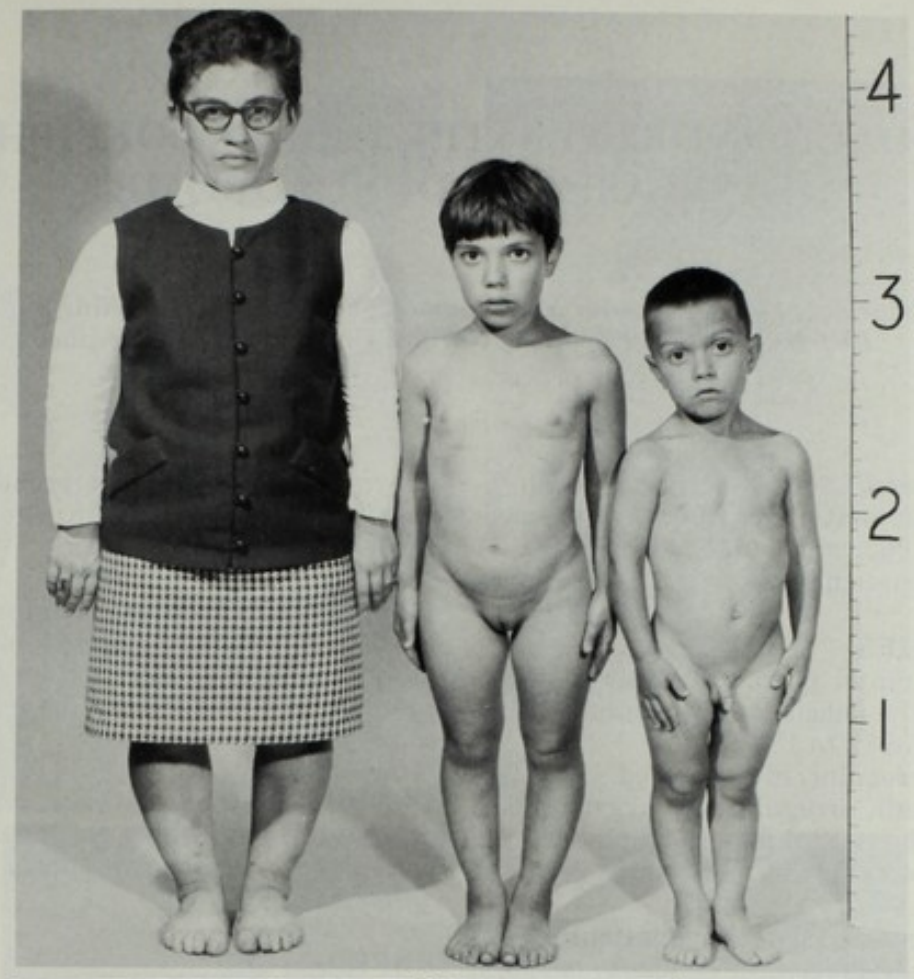
NATURAL HISTORY. Slow growth, if not evident by birth, is usually obvious by three years of age. Final height attainment in adults[3, 4] ranged from 46.5 to 60 inches. Outward bowing of the lower limbs and genu varum may become pronounced with weight bearing. Though this may improve in childhood, it may merit surgical straightening. The relatively long fibulae can result in inversion of the feet. Exercise may provoke mild aching in the knees, ankles, and/or elbows during childhood and such discomfort is usually worse and may include the low back in the adult. Caesarian section is often required for delivery in the pregnant woman with this disorder.

Mental deficiency, a rare feature in achondroplasia, was noted in four of the 13 cases reported by Walker, et al.[3] The cause of the mental deficiency, which ranged from intelligence quotients of 50 to 80 in these four cases, is unknown.

ETIOLOGY. Autosomal dominant mutant gene etiology has been implicated by direct inheritance from affected individuals and by older paternal age among the presumed fresh mutation cases from unaffected parents, which represent the majority of cases.

REFERENCES

1. Ravenna, F.: Achondroplasie et chondrohypoplasie: Contribution clinique. N. Iconog. Salpêtrière, *26*:157, 1913.
2. Léri, A., and Linossier, (Mlle.): Hypochondroplasie héréditaire. Bull. Mem. Soc. Med. Hop. (Paris), *48*:1780, 1924.
3. Walker, B. A., Murdoch, J. L., McKusick, V. A., Langer, L. O., and Beals, R. K.: Hypochondroplasia. Am. J. Dis. Child., *122*:95, 1971.
4. Beals, R. K.: Hypochondroplasia. A report of five kindreds. J. Bone Joint Surg. [Am.], *51*:728, 1969.





Above, Affected mother and children (seven and six years) showing short stature, most striking in the bowed lower limbs.

Lower left, Note slight ulnar shortening, metaphyseal flaring with bulbous radial enlargement, and elongation of the styloid process (from a ten year old).

Lower middle, Seven year old showing elongation of distal fibula and slight "squaring off" of the proximal tibial epiphysis.

Lower right, Adult showing more striking squaring of proximal tibial epiphysis with sharp flare of metaphysis and elongation of distal fibula with varus deformity of ankle mortise. (From Beals, R. K.: J. Bone Joint Surg. [Am.], *51*:728, 1969.)

PSEUDOACHONDROPLASTIC SPONDYLOEPIPHYSEAL DYSPLASIA (SED) SYNDROME

Small Irregular Epiphyses, Irregular Mushroomed Metaphyses, Flattening and/or Anterior Beaking of Vertebrae, with Normal Craniofacial Appearance

Maroteaux and Lamy[1] described three individuals with this pattern of altered bone morphogenesis in 1963, and subsequently at least four additional cases have been published.[2-5]

ABNORMALITIES

Growth. Apparently postnatal onset of short-limb growth deficiency by second year. Adult stature 82 to 130 cm.

Metaphyses. Irregular, mushroomed.

Epiphyses. Small, irregular or "fragmented," especially the capital femora epiphysis.

Diaphyses. Short, bowing, especially in lower extremities.

Vertebrae. Variable degrees of flattening, anterior tongue-shaped, and short pedicles. Lumbar lordosis, kyphosis, scoliosis.

Ribs. Tend to be spatulate.

Joints. Hypermobility of major joints except elbows.

OCCASIONAL ABNORMALITIES. Pelvis: short sacroiliac notch, flaring of iliac crests.

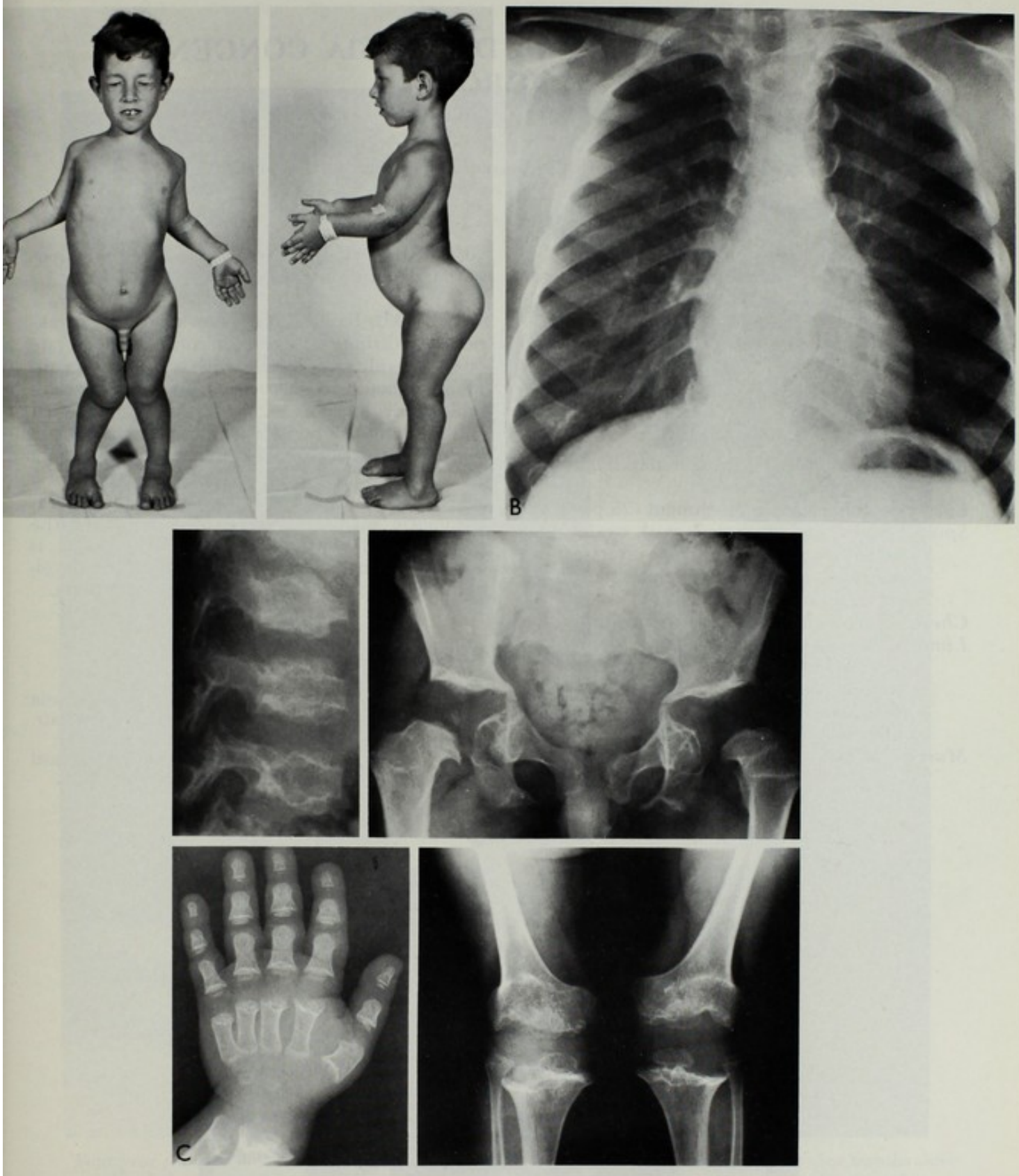
NATURAL HISTORY. The patients have been described as "normal" at birth, with small size and waddling gait becoming evident between six months and four years of age. Bowed lower extremities with waddling gait and scoliosis are the principal orthopedic problems, and there may be some limitation in joint motility. Intelligence is normal.

ETIOLOGY. Apparently autosomal dominant, Ford, et al.[2] having reported a father and his two affected offspring. Most of the cases have been sporadic and presumably represent fresh mutations.

COMMENT. The postnatal onset and normal craniofacial appearance readily differentiate this entity from true achondroplasia.

REFERENCES

1. Maroteaux, P., and Lamy, M.: Les formes pseudoachondroplasiques des dysplasies spondyloépiphysaires. Presse Med., *67*:383, 1959.
2. Ford, N., Silverman, F. N., and Kozlowski, K.: Spondylo-epiphyseal dysplasia (pseudoachondroplastic type). Am. J. Roentgenol. Radium Ther. Nucl. Med., *86*:462, 1961.
3. Rubin, P.: Achondroplasia versus pseudoachondroplasia. Radiol. Clin. North. Am., *1*:621, 1963.
4. Lindseth, R. E., Danigelis, J. A., Murray, D. G., and Wray, J. B.: Spondylo-epiphyseal dysplasia (pseudoachondroplastic type). Case report with pathologic and metabolic investigations. Am. J. Dis. Child., *113*:721, 1967.



A, Eight year old with height age of three years.

B, Mildly spatulate ribs; scoliosis

C, Flattened irregular vertebral bodies, hypoplastic abnormal iliac wings, and short tubular bones with irregular "ball-in-socket" epiphyses in relation to metaphyses.

(From Lindseth, R. E., et al.: Am. J. Dis. Child., *113*:721, 1967.)

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA SYNDROME

Short Trunk, Lag in Epiphyseal Mineralization, Myopia

Spranger and Wiedemann[1] established this disorder in 1966 when they reported six new cases and summarized 14 from the past literature.

ABNORMALITIES

Growth. Prenatal onset growth deficiency, final height 37 to 52 inches.

Facies. Variable flat facies, malar hypoplasia, cleft palate.

Eye. Myopia, retinal detachment (25 per cent).

Spine. Short, including neck with ovaloid flattened vertebrae with narrow intervertebral disc spaces, odontoid hypoplasia, kyphoscoliosis, and lumbar lordosis.

Chest. Barrel chest with pectus carinatum.

Limbs. Lag in mineralization of epiphyses, which tend to be flat, with no os pubis, talus, calcaneus, or knee centers mineralized at birth. Coxa vara. Diminished joint mobility at elbows, knees, and hips.

Muscle. Weakness, easy fatigability, hypoplasia of abdominal muscles.

OCCASIONAL ABNORMALITIES. Talipes varus, dislocation of hip.

NATURAL HISTORY. The hypotonic weakness and orthopedic situation contribute to a late onset of walking, usually with a waddling gait. Myopia should be suspect and frequent ophthalmologic evaluation is merited to guard against retinal detachment. Morning stiffness may be a feature, but there is usually no undue joint pain.

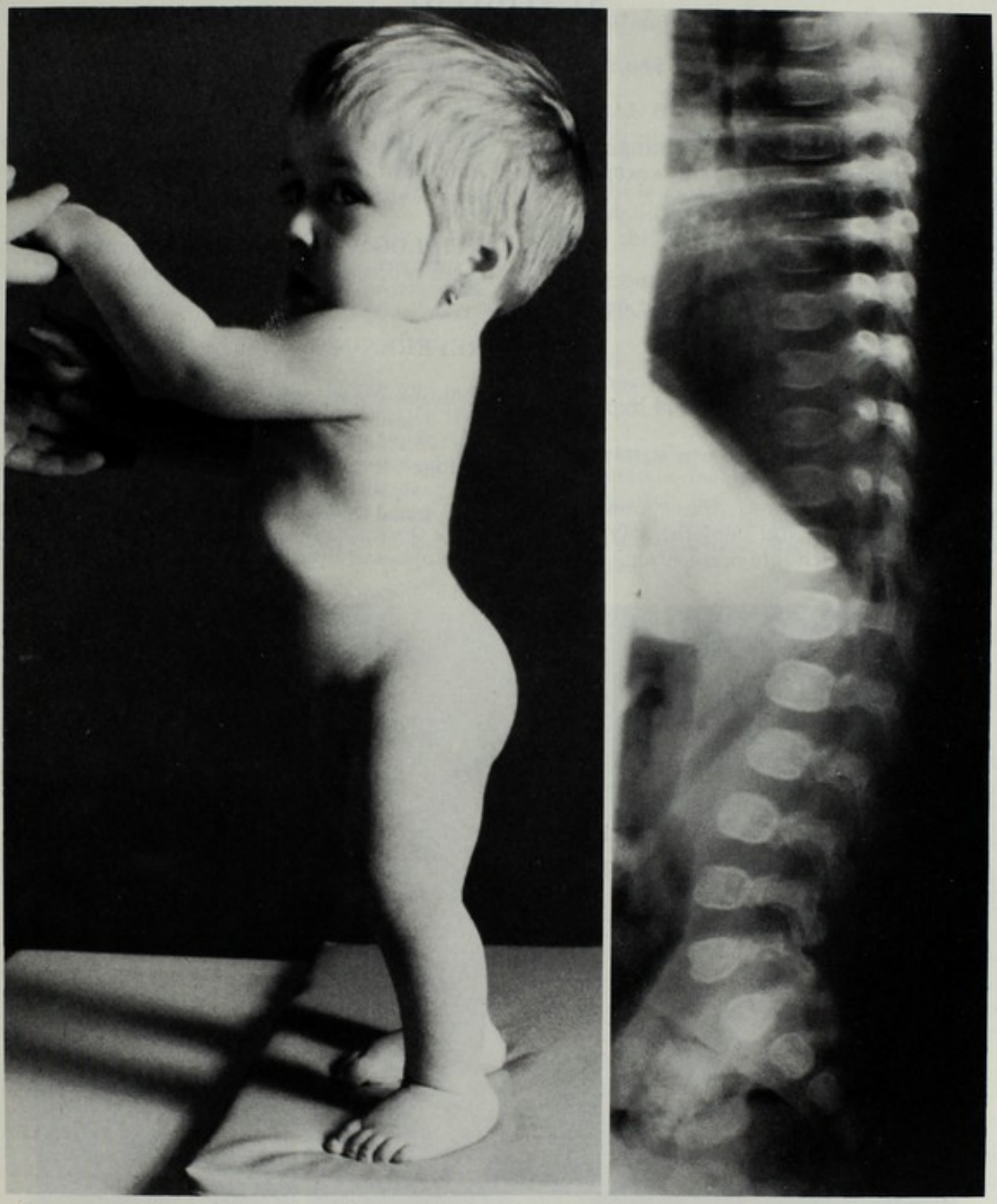
ETIOLOGY. Autosomal dominant. Fine metachromatic inclusions have been noted in the lymphocytes; however, the metabolic defect is unknown. There is hypocellularity of the developing cartilage, especially at the growth plate.

REFERENCES

1. Spranger, J., and Wiedemann, H. R.: Dysplasia spondyloepiphysaria congenita. Helv. Paediatr. Acta, *21*:598, 1966.
2. Spranger, J., and Langer, L. O.: Spondyloepiphyseal dysplasia congenita. Radiology, *94*:313, 1970.



Pelvis at seven years showing horizontal acetabula and lack of ossification of femoral heads and femoral necks, which are in severe varus position. (From Dr. Jurgen Spranger, Mainz, Germany.)



Four year old boy. Note the flat midface and lumbar lordosis. Roentgenogram of spine at nine months showing mild dorsal flattening and minimal beaking at L2-L3. (From Dr. Jurgen Spranger, Mainz, Germany.)

KOZLOWSKI SPONDYLOMETAPHYSEAL DYSPLASIA SYNDROME

Early Childhood Onset Short Spine, Irregular Metaphyses, Pectus Carinatum

Kozlowski, Maroteaux, and Spranger[1] established this disorder in 1967 and several additional cases have been recognized.[2, 3]

ABNORMALITIES

Growth. Growth deficiency, especially of trunk, from one to four years of age. Adult height 4 feet 3 inches to 5 feet.

Spine. Short neck and trunk with dorsal kyphosis. Platyspondyly with anterior narrowing in lumbar region. Odontoid hypoplasia.

Thorax. Pectus carinatum.

Pelvis. Squarish, short iliac wings, flat, irregular acetabula.

Limbs. Irregular ricketic-like metaphyses, especially the distal femoral. Hypoplastic carpal bones with late ossification.

NATURAL HISTORY. Waddling gait with limitation of joint mobility and early degenerative joint changes leading to discomfort.

ETIOLOGY. Autosomal dominant with most cases representing fresh mutation.

REFERENCES

1. Kozlowski, K., Maroteaux, P., and Spranger, J.: La dysostose spondylo-métaphysaire. Presse Med., *75*:2769, 1967.
2. Riggs, W., Jr., and Summitt, R. L.: Spondylometaphyseal dysplasia (Kozlowski). Report of affected mother and son. Radiology, *101*:375, 1971.
3. Le Quesne, G. W., and Kozlowski, K.: Spondylometaphyseal dysplasia. Br. J. Radiol., *46*:685, 1973.



Young boy. Note bowed legs, flattened vertebrae, and metaphyseal flare. (From Riggs, W., Jr., and Summitt, R. L.: Radiology, *101*:375, 1971.)

METATROPIC DWARFISM SYNDROME

Small Thorax, Thoracic Kyphoscoliosis, Metaphyseal Flaring

Maroteaux, Spranger, and Wiedemann[1] set this entity forth with five cases of their own and 12 unrecognized cases from the literature.

ABNORMALITIES.[1] Small stature, severe.

Skeletal. Early platyspondyly with progressive kyphosis and scoliosis in infancy to early childhood.

Narrow thorax with short ribs.

Short limbs with metaphyseal flaring and epiphyseal irregularity with hyperplastic trochanters. Prominent joints with restricted mobility at knee and hip but increased extensibility of finger joints.

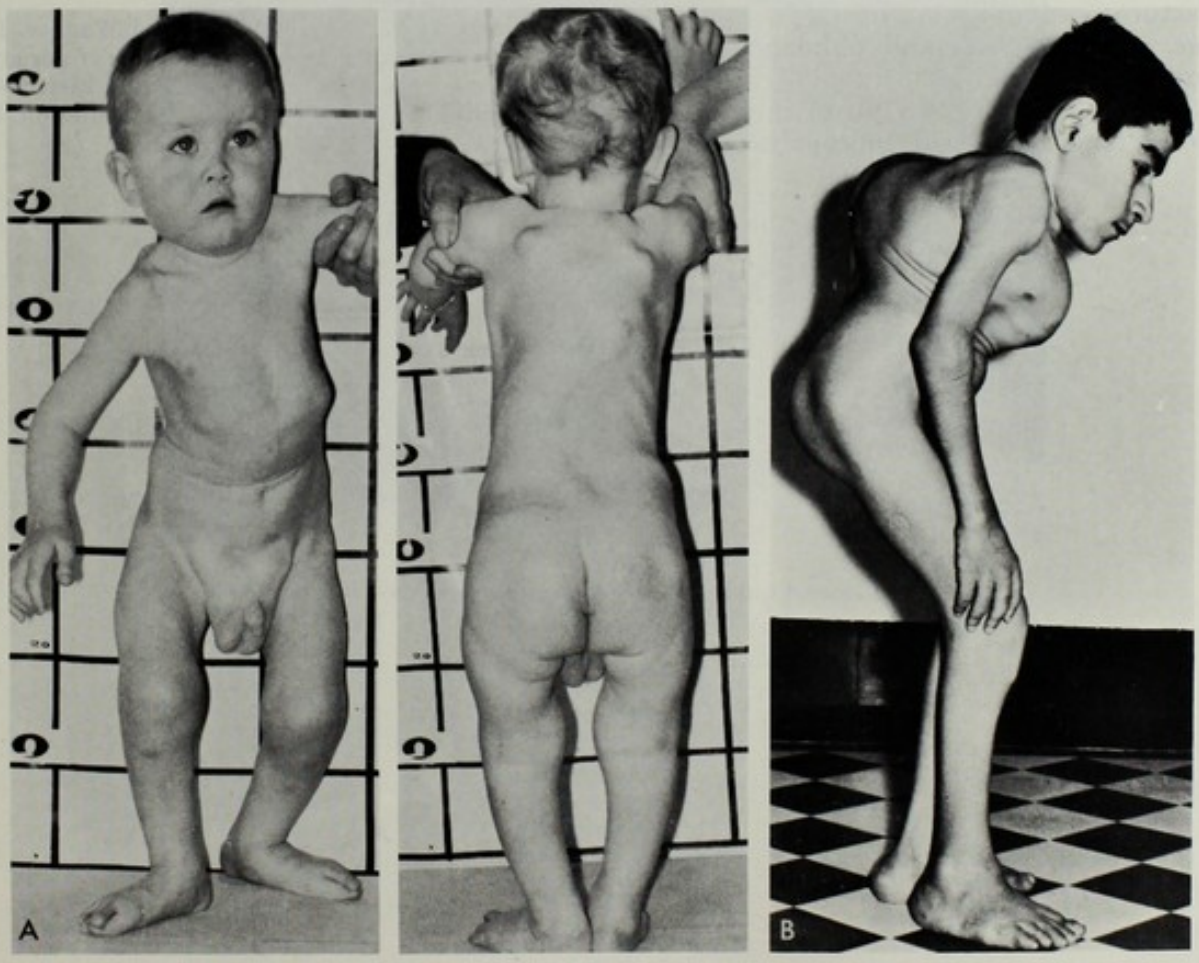
Hypoplasia of basilar pelvis with horizontal acetabula, short deep sacroiliac notch, and squared iliac wings.

NATURAL HISTORY. Often evident at birth, the vertebral changes are severe during infancy.

ETIOLOGY. Apparently both autosomal dominant and autosomal recessive inheritance can occur for this disorder.

REFERENCES

1. Maroteaux, P., Spranger, J., and Wiedemann, H. R.: Der metatropische Zwergwuchs. Arch. Kinderheilkhd., *173*:211, 1966.
2. Fleury, J., de Menibus, C. H., and Hazard, E.: Un cas singulier de dystrophie ostéo-chondrale congénitale (nanisme métatropique de Maroteaux). Ann. Pediatr. (Paris), *13*:453, 1966.
3. Larose, J. H., and Gay, B. G.: Metatropic dwarfism. Am. J. Roentgenol. Radium Ther. Nucl. Med., *106*:156, 1969.



A, A two year old.
B, A 16 year old.
(Courtesy of P. Maroteaux, Hospital des Enfants-Malades, Paris.)

GELEOPHYSIC DWARFISM SYNDROME

Coarse Pleasant Facies, Short Hands and Feet, Joint Contractures

Spranger, et al.[1] described this disorder in an unrelated boy and girl in 1971 and suggested that a case previously reported by Vanace, et al.[2] might represent the same condition.

ABNORMALITIES

Growth. Progressive deficiency, ? of prenatal onset.

Facies. Thick, long upper lip with flattened philtrum, short nose with anteverted nostrils. "Pleasant, happy-natured" appearance.

Skin. Relatively thickened and "tight," especially in paraspinal area.

Skeletal and Joints. Short hands and feet. Dysostosis multiplex congenita-like changes with short tubular bones, especially first metacarpal, proximal pointing of second through fifth metacarpals, and ovoid-shaped vertebrae in thoracolumbar area. Joint contractures, especially in fingers.

Cardiac. Thick mitral and pulmonic valves, cardiomegaly.

Liver. Hepatomegaly (two out of three cases).

Metabolic. Lack of acid mucopolysaccharide (AMPS) excess in urine, with focal excess AMPS (?dermatan sulfate) storage in liver, heart.

NATURAL HISTORY. These patients are apparently of normal intelligence but are liable to respiratory infections, including pneumonia, and one died at five years of age with cardiac failure. The joint contractures partially limit function.

ETIOLOGY. ?Autosomal recessive.

REFERENCES

1. Spranger, J. W., Gilbert, E. F., Tuffli, G. A., Rossiter, F. P., and Opitz, J. M.: Geleophysic dwarfism—a "focal" mucopolysaccharidosis? Lancet, *2*:97, 1971.
2. Vanace, P. W., Friedman, S., and Wagner, B. M.: Mitral stenosis in an atypical case of gargoylism: A case report with pathologic and histochemical studies of the cardiac tissues. Circulation, *21*:80, 1960.



Two year old boy. (From Spranger, J. W., et al.: Lancet, 2:97, 1971.)

ELLIS-VAN CREVELD SYNDROME

(Chondroectodermal Dysplasia Syndrome)

Short Distal Extremities, Polydactyly, Nail Hypoplasia

Ellis and van Creveld[1] set forth this entity in 1940. About 40 cases were reported by 1964 when McKusick, et al.[2] added 52 cases from an inbred Amish population.

ABNORMALITIES

Growth. Small stature of prenatal onset.

Skeletal. Disproportionate irregularly short extremities.
Polydactyly of fingers, occasionally of toes.
Fusion of hamate and capitate.
Small thorax.
Hypoplasia of upper lateral tibia with knock knee.

Nails. Hypoplastic.

Teeth. Neonatal teeth, partial anodontia, small teeth, and/or delayed eruption.

Mouth. Short upper lip bound by frenula to alveolar ridge, defects in alveolar ridge with accessory frenula.

Cardiac. About one half of patients have a cardiac defect, most commonly an atrial septal defect.

OCCASIONAL ABNORMALITIES. Mental retardation, scant or fine hair, cryptorchidism, epispadias, talipes equinovalgus.

NATURAL HISTORY. About half the patients die in early infancy as a consequence of cardiorespiratory problems. The majority of survivors are of normal intelligence. Eventual stature is in the range of 43 to 60 inches. There is usually some limitation in hand function such as inability to form a clenched fist. Dental problems are frequent.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Ellis, R. W. B., and van Creveld, S.: A syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and congenital morbus cordis. Report of three cases. Arch. Dis. Child., *15*:65, 1940.
2. McKusick, V. A., Egeland, J. A., Eldridge, R., and Krusen, D. E.: Dwarfism in the Amish. The Ellis-van Creveld syndrome. Bull. Hopkins Hosp., *115*:306, 1964.
3. Feingold, M., Jankoski, J., Johnson, C., Darling, D. B., Kreidberg, M. B., Wilson, D., Cohen, M. M., and Gellis, S. S.: Ellis-van Creveld syndrome. Clin. Pediatr. (Phila.), *5*:431, 1966.



A, Six week old. Note the hypoplasia of the alveolar ridge with frenula and an aberrant tooth. The patient is now doing well at several years of age.

B, Five month old. Note the small thorax. The patient expired as a consequence of a congenital heart defect plus the small thorax. (Courtesy of Professor H. Willi, Kantonsspital, Zurich.)

DIASTROPHIC* DWARFISM SYNDROME

(Diastrophic Nanism Syndrome)

Short Tubular Bones (Especially First Metacarpal), Joint Limitation with Club Foot, and Hypertrophied Auricular Cartilage

The 1960 report of Lamy and Maroteaux[1] concerning three cases of their own and 11 similar cases from the literature established this pattern of malformation as a distinct entity. It is now being recognized with increasing frequency.

ABNORMALITIES

Growth. Short stature of prenatal onset. Mean birth length 13 inches. Average adult stature 44 inches, with range from 34 to 50 inches.

Limbs. Varus club foot plus limitation of flexion at proximal phalangeal joints and of extension at elbow, with or without dislocation of hip or knee with weight bearing.

Tubular bones short and thick with development of broad metaphyses and flattened irregular epiphyses that are late in mineralizing. Carpal bones may be accelerated in ossification in contrast to the remainder of the hand. First metacarpal unduly small with proximal thumb. Variable symphalangism of proximal interphalangeal joints. Variable webbing at joints.

Spine. Development of scoliosis with or without kyphosis.

Pinna. Soft cystic masses in auricle develop into hypertrophic cartilage in early infancy in 84 per cent of patients.

OCCASIONAL ABNORMALITIES. Thick pectinate strands at root of iris, cleft palate (one fourth), micrognathia, lateral displacement of patellae, subluxation of cervical vertebrae, elbow dislocation of head of radius, hyperelasticity of skin, cryptorchidism. Early mineralization of ribs, intracranial calcification. Deafness secondary to fusion or lack of ossicles, stenosis of the external auditory canal. Laryngotracheal stenosis. Capillary hemangiomata, midface.

NATURAL HISTORY. Two affected infants with cleft palate and micrognathia, similar in this respect to those with the Robin anomalad, died of respiratory obstruction. The mortality related to respiratory obstruction, including laryngeal stenosis, can be as high as 25 per cent in early infancy. For the survivors general health is usually good and the patients have normal intelligence. Unfortunately the varus club foot and the scoliosis that develop have been rather resistant to corrective orthopedic measures and the functional problem is augmented by the limitation in joint motility. Spinal cord compression may occur as a consequence of severe kyphoscoliosis. When present, the unusual defect of hypertrophied auricular cartilage may eventually give way to ossification.

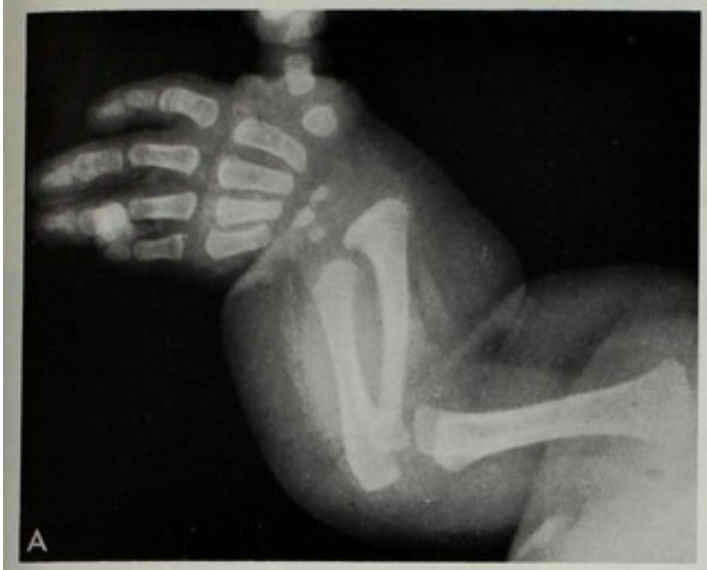
ETIOLOGY. Autosomal recessive.

COMMENT. Diastrophic dwarfism can readily be distinguished from other chondrodystrophies and from arthrogryposis multiplex congenita by physical examination alone.

*Diastrophic = crooked.

REFERENCES

1. Lamy, M., and Maroteaux, P.: Le nanisme diastrophique. Presse Med., *68*:1977, 1960.
2. Langer, L. O.: Diastrophic dwarfism in early infancy. Am. J. Roentgenol. Radium Ther. Nucl. Med., *93*:399, 1965.
3. Walker, B. A., Scott, C. I., Hall, J. G., Murdoch, J. L., and McKusick, V. A.: Diastrophic dwarfism. Medicine, *51*:41, 1972.





A, Diastrophic dwarfism in four month old. Note small first metacarpal.

B, One month old. Note cystic swelling of ear. (From Langer, L. O.: Am. J. Roentgenol. Radium Ther. Nucl. Med., *93*:399, 1965.)

C, Twenty one month old. Note hypertrophy of ear and position of thumbs. (From Smith, D. W.: J. Pediatr., *70*:502, 1967.)







X-LINKED SPONDYLOEPIPHYSEAL DYSPLASIA SYNDROME

Flattened Vertebrae of Mid-Childhood, Small Iliac Wings, Short Femoral Neck

This disorder was recognized in 1939 by Jacobsen.[1]

ABNORMALITIES. Onset between five and ten years of age.

Growth. Short stature; final height, 52 to 62 inches.

Spine. Flattened vertebrae with central hump. Kyphosis, mild scoliosis, short neck.

Pelvis. Small iliac wings.

Limbs. Short femoral neck.

Mild epiphyseal irregularity with flattening of femoral head.

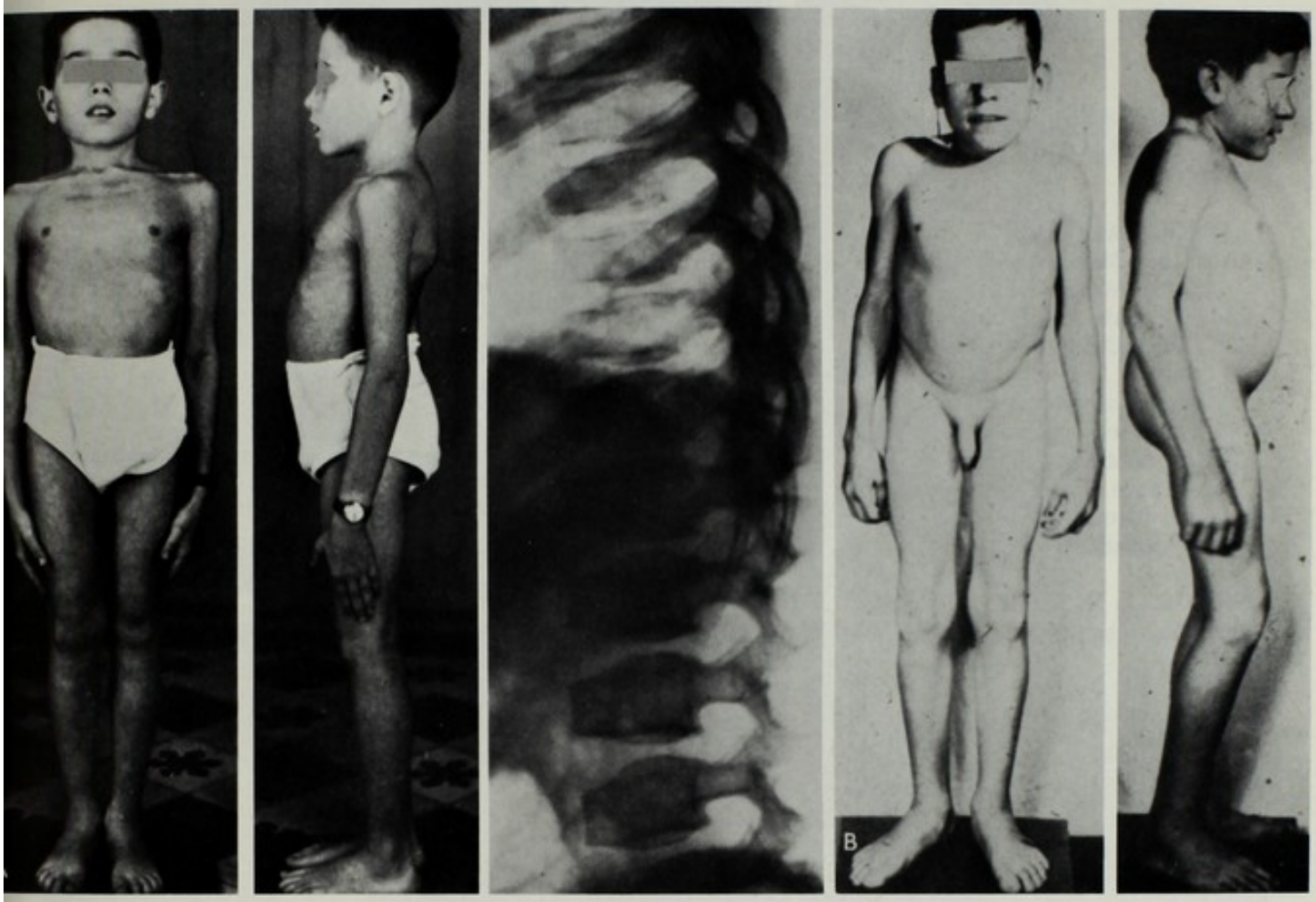
Joints. Eventual hip pain and stiffness, back pain.

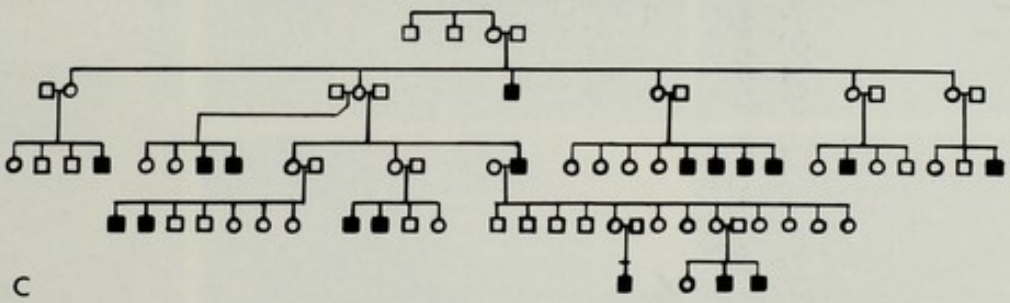
NATURAL HISTORY. Shortening of trunk. Back, knee, and especially hip pain due to osteoarthritis by 40 years of age; often disabling by 60 years.

ETIOLOGY. X-linked recessive.

REFERENCES

1. Jacobsen, A. W.: Hereditary osteochondrodystrophia deformans. A family with twenty members affected in five generations. J.A.M.A., *113*:121, 1939.
2. Maroteaux, P., Lamy, M., and Bernard, J.: La dysplasie spondylo-epiphysaire tardive. Description clinique et radiologique. Presse Med., *65*:1205, 1957.
3. Langer, L. O.: Spondyloepiphyseal dysplasia tarda. Hereditary chondrodysplasia with characteristic vertebral configuration in the adult. Radiology, *82*:833, 1964.
4. Bannerman, R. M., Ingall, G. B., and Mohn, J. F.: X-linked spondyloepiphyseal dysplasia tarda. J. Med. Genet., *8*:291, 1971.





A, Twelve year old. Note shortening of trunk due to flattened vertebrae, each of which has a central "hump" in the area of its epiphyses. (Courtesy of P. Maroteaux, Hospital for Sick Infants, Paris.)

B, Fifteen year old. (From Jacobsen, A. W.: J.A.M.A., *113*:121, 1939.)

C, Pedigree of which patient shown in *B* is a member, showing evidence of X-linked recessive inheritance. (Courtesy of R. Bannaman, Buffalo General Hospital.)

MULTIPLE EPIPHYSEAL DYSPLASIA SYNDROME

Small Irregular Epiphyses, Pain and Stiffness in Hips, Short Stature

This condition was described by Fairbank[1] in 1947 and is often difficult to diagnose with assurance.

ABNORMALITIES

Growth. Mild to moderate shortness of stature. Adult stature 145 to 170 cm.

Limbs. Late ossifying, small, irregular, mottled epiphyses with eventual osteoarthritis due to loss of articular cartilage in many large joints, especially in hips and knees. Short femoral neck.

Mild metaphyseal flare.

Shortness of metacarpals and phalanges.

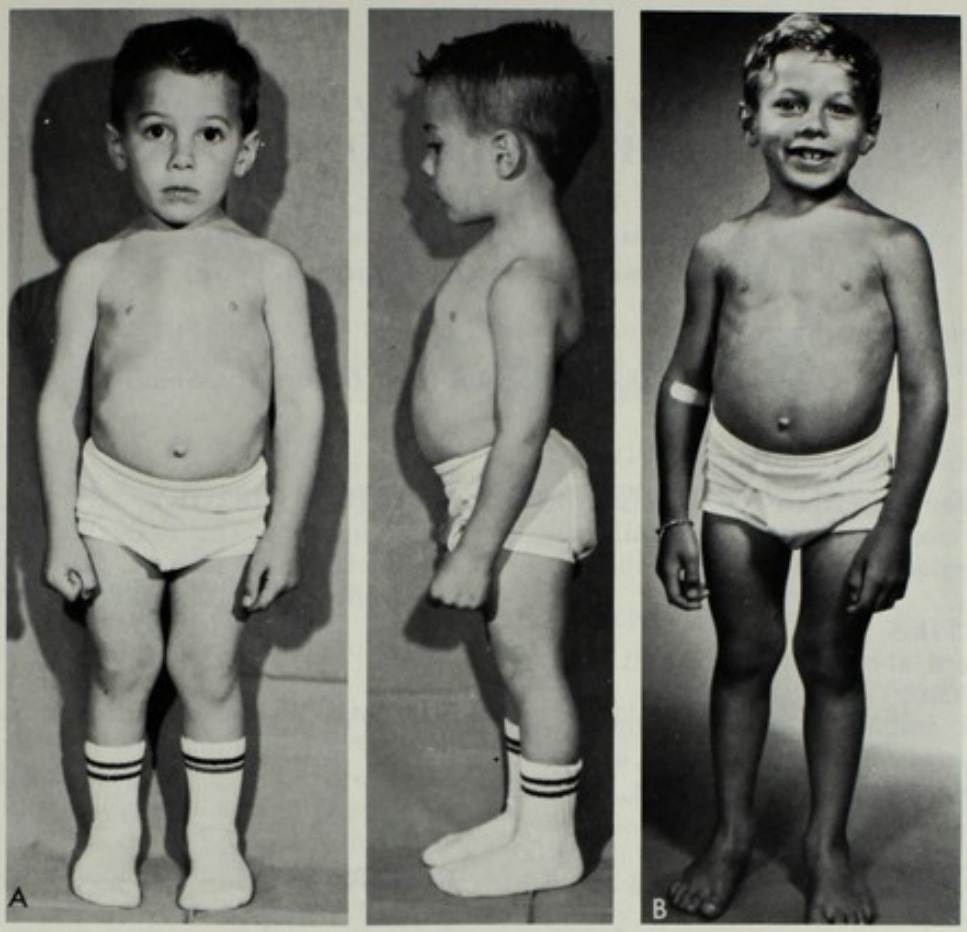
Spine. Blunted, slightly ovaloid, sometimes flattened vertebral bodies.

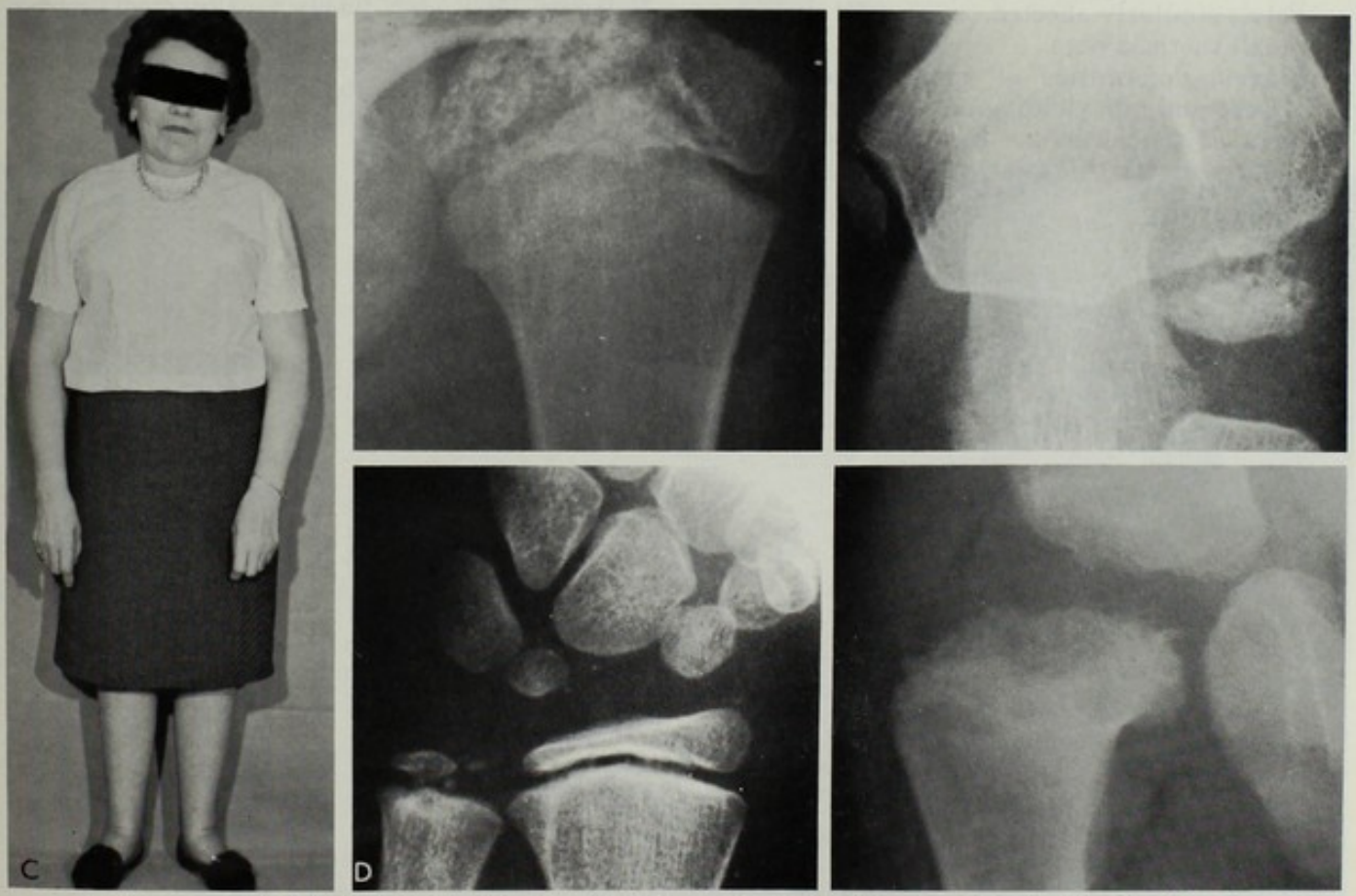
NATURAL HISTORY. Evident by two to ten years because of waddling gait and slow growth. Pain and stiffness in joints, particularly the hips, may be a complaint as early as five years, but usually not until 30 to 35 years.

ETIOLOGY. Autosomal dominant with wide variability in expression.

REFERENCES

1. Fairbank, T.: Dysplasia epiphysealis multiplex. Brit. J. Surg., *34*:225, 1947.
2. Maudsley, R. H.: Dysplasia epiphysialis multiplex. A report of fourteen cases in three families. J. Bone Joint Surg. [Am.], *37B*:228, 1955.
3. Hoefnagel, D., Sycamore, L. K., Russell, S. W., and Bucknall, W. E.: Hereditary multiple epiphyseal dysplasia. Ann. Hum. Genet., *30*:201, 1967.





A, Five year old with height age of two and one half years. Patient had occasional aching in legs.

B, Same patient at eight and one half years; height age, four and one half years. He now has ankle and hip discomfort.

C, Affected mother of patient shown in *A* and *B*. She is short of stature and has hip discomfort.

D, Late and irregular mineralization of epiphyses which may be small or aberrant in shape, or both.

JANSEN METAPHYSEAL CHONDRODYSPLASIA SYNDROME

(Metaphyseal Dysostosis, Jansen-Type)

Wide Irregular Metaphyses, Flexion Joint Deformity, Small Thorax

Since Jansen[1] described this severe type of metaphyseal dysostosis, only a few similar cases have been recorded, as reviewed by Rubin.[2]

ABNORMALITIES

Growth. Severe short stature. Adult stature about 125 cm.

Facies. Small, immature in appearance, with prominent eyes. Mild supraorbital and frontonasal hyperplasia in the adult. Micrognathia.

Skeletal and Joint. Gross irregular cyst-like areas due to lack of metaphyseal ossification.

Pelvis similarly affected.

Small thoracic cage.

Flexion deformities of joints, especially at knee and hip, yielding a squatting stance.

Other. Hypercalcemia, hyperostosis of calvarium with thick dense base of skull. Variable deafness.

NATURAL HISTORY. Evident at birth or in early infancy. The defective growth and joint dysfunction are severe. Mental deficiency is mentioned, but not well documented.

ETIOLOGY. Autosomal dominant, most cases being fresh mutations.

REFERENCES

1. Jansen, M.: Über atypische Chondrodystrophie (Achondroplasie) und über eine noch nicht beschriebene angeborne Wachstrumsstörung des Knochensystems: Metaphysäre Dysostosis. 2. Orthop. Chir., *61*:253, 1934.
2. Rubin, P.: Dynamic Classification of Bone Dysplasias. Chicago, Year Book Medical Publishers, 1964, p. 207.





Affected mother and daughter. (From W. Lenz, Münster, Germany.)

SCHMID METAPHYSEAL CHONDRODYSPLASIA SYNDROME

(Metaphyseal Dysostosis, Schmid-Type)

Since the initial description by Schmid[1] in 1949, several large pedigrees of affected individuals have been reported.[2, 3]

ABNORMALITIES

Growth. Mild to moderate shortness of stature. Adult height 130 to 160 cm.

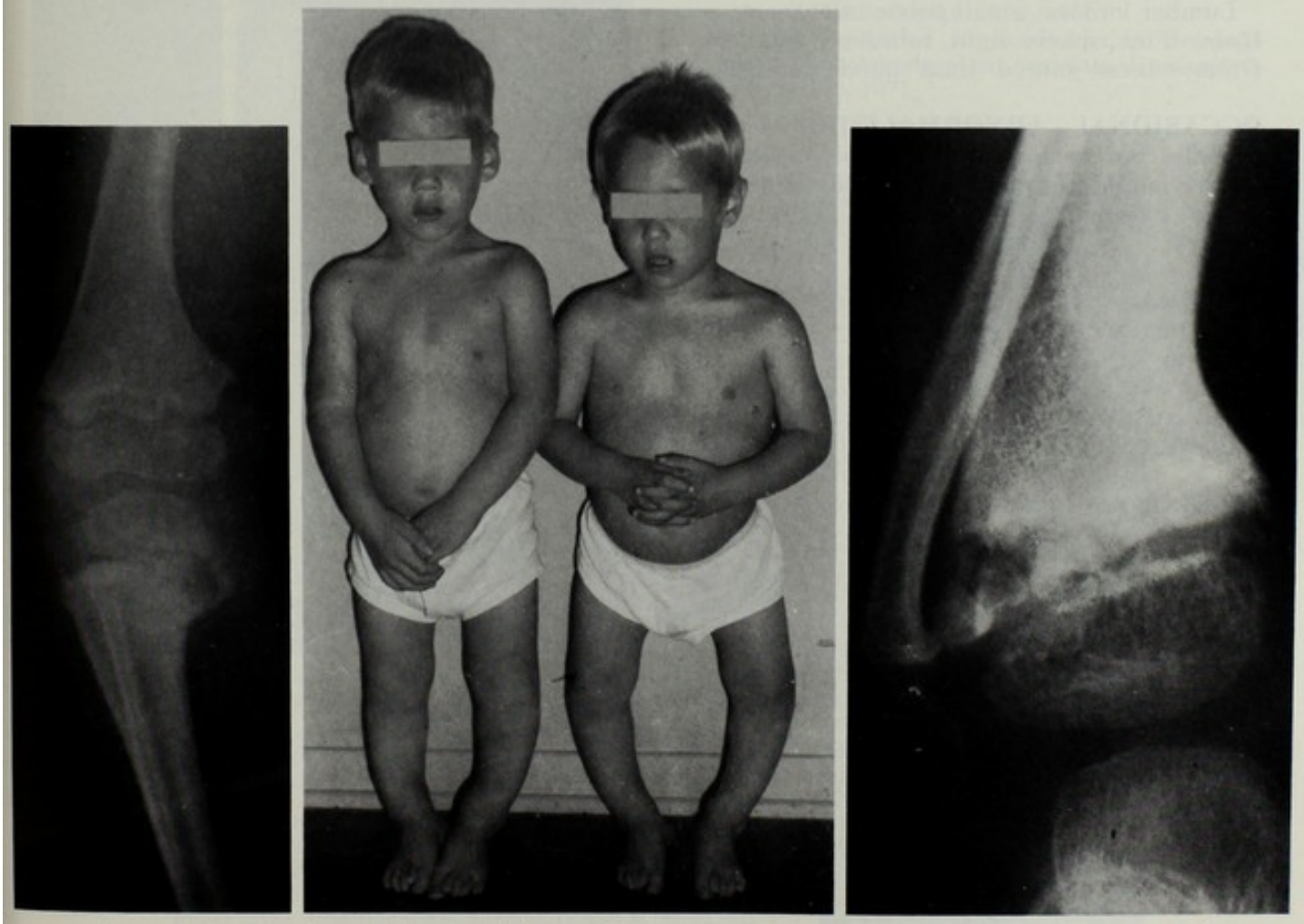
Skeletal. Splaying of broad irregular metaphyses. Relatively short tubular bones.
Tibial bowing, especially at ankle.
Waddling gait with coxa vara and genu vara.
Flare to lower rib cage.
Mild limitation in full extension of fingers.

NATURAL HISTORY. Short stature and bowed legs usually evident in second year. Pain in legs during childhood. Symptomatic and radiographic improvement beginning as early as three years of age with orthopedic measures only indicated for unusual degrees of deformity and usually not until growth is complete. Since the epiphyses are not affected there are usually no osteoarthritic symptoms.

ETIOLOGY. Autosomal dominant with variable expression. Biopsy discloses cartilage hypoplasia.

REFERENCES

1. Schmid, F.: Beitrag zur Dysostosis Enchondralis Metaphysaria. Monatsschr. Kinderheilkd., *97*:393, 1949.
2. Stickler, G. B., Maher, F. T., Hunt, J. C., Burke, E. C., and Rosevear, J. W.: Familial bone disease resembling rickets (hereditary metaphysial dysostosis). Pediatrics, *29*:996, 1962.
3. Rosenbloom, A. L., and Smith, D. W.: The natural history of metaphyseal dysostosis. J. Pediatr., *66*:857, 1965.



Affected brothers showing bowing of legs, mild changes in thorax, and metaphyseal alterations. (From Rosenbloom, A. L., and Smith, D. W.: J. Pediatr., *66*:857, 1965.)

CARTILAGE-HAIR HYPOPLASIA SYNDROME

(McKusick Metaphyseal Chondrodysplasia Syndrome)

Mild Bowing of Legs, Wide Irregular Metaphyses, Fine Sparse Hair

Discovered by McKusick, et al.[1] among an inbred Amish population, this condition has subsequently been detected in non-Amish individuals.

ABNORMALITIES

Growth. Small stature; adult height, 107 to 147 cm.

Skeletal. Irregular scalloped metaphyses. Relatively short limbs, mild bowing of legs.
Short tibia in relation to fibula. Prominent heel. Flat feet.
Short hands, fingernails, toenails.
Decreased height of vertebrae.
Incomplete extension of elbow.
Mild flaring of lower rib cage with prominent sternum.
Lumbar lordosis, small pelvic inlet.

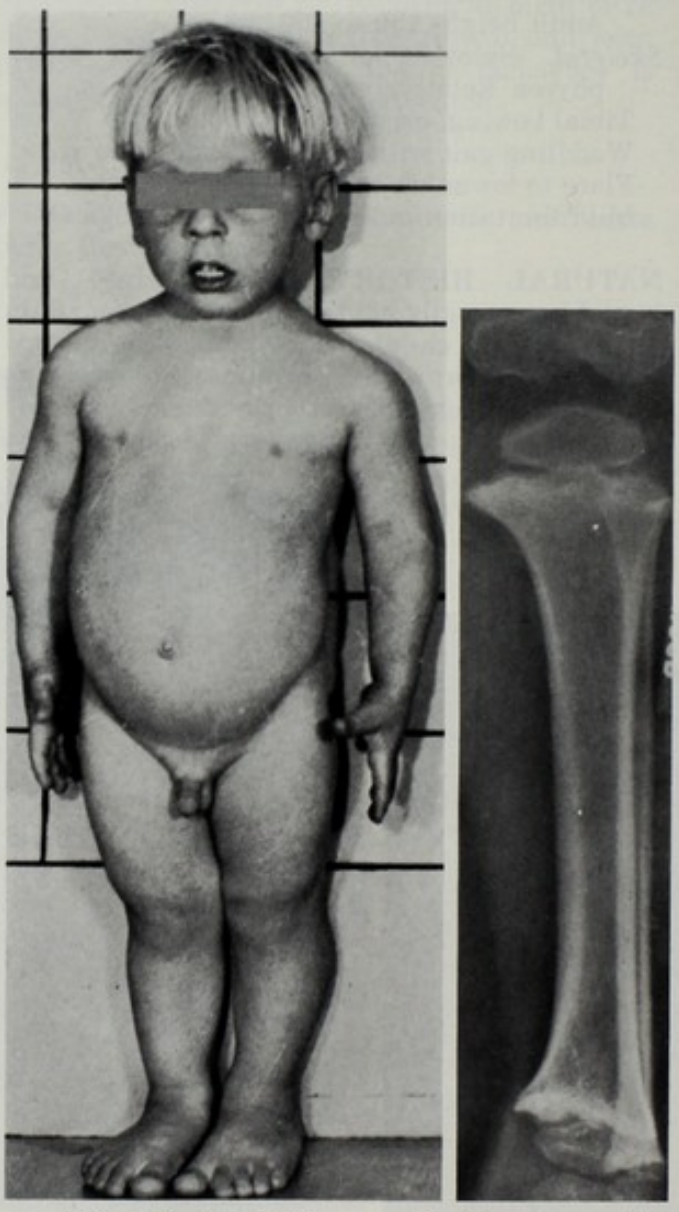
Hair. Fine, sparse, light, relatively fragile.

Other. Loose jointed "limp" hands and feet.

OCCASIONAL ABNORMALITIES. Brachycephaly. Severe or fatal response to varicella with lymphopenia and diminished cellular immune response. Intestinal malabsorption in infancy.

NATURAL HISTORY. The early history is often indicative of an intestinal malabsorption problem, which tends to improve with time. Biopsy of the metaphyseal area reveals diminished cartilage cells forming poorly organized columns.

ETIOLOGY. Autosomal recessive.



Five and one half year old; height age, 18 months. (From McKusick, V. A., et al.: Bull. Hopkins Hosp., *116*:285, 1965.)

REFERENCES

1. McKusick, V. A., Eldridge, R., Hostetler, J. A., Ruangwit, U., and Egeland, J. A.: Dwarfism in the Amish. II. Cartilage-hair hypoplasia. Bull. Hopkins Hosp., *116*:285, 1965.
2. Lux, S. E., et al.: Chronic neutropenia and abnormal cellular immunity in cartilage-hair hypoplasia. N. Engl. J. Med., *282*:231, 1970.

CONRADI-HÜNERMANN SYNDROME

(Chondrodysplasia Punctata, Autosomal Dominant)

Asymmetrical Limb Shortness, Early Punctate Mineralization, Large Skin Pores

Initially described by Conradi[1] and later by Hünermann,[2] this disorder was clearly distinguished from the autosomal recessive type of chondrodysplasia punctata by Spranger, et al.[3]

ABNORMALITIES

Growth. Mild to moderate growth deficiency.

Facies. Variable low nasal bridge with flat facies, hypoplasia of malar eminences with downslanting palpebral fissures.

Limbs. Asymmetrical shortening related to areas of punctate mineralization in epiphyses. Variable joint contractures.

Spine. Frequent scoliosis, even in infancy, related to areas of punctate mineralization.

Skin. Variable follicular atrophoderma with large pores resembling "orange peel." Sparse hair which tends to be coarse.

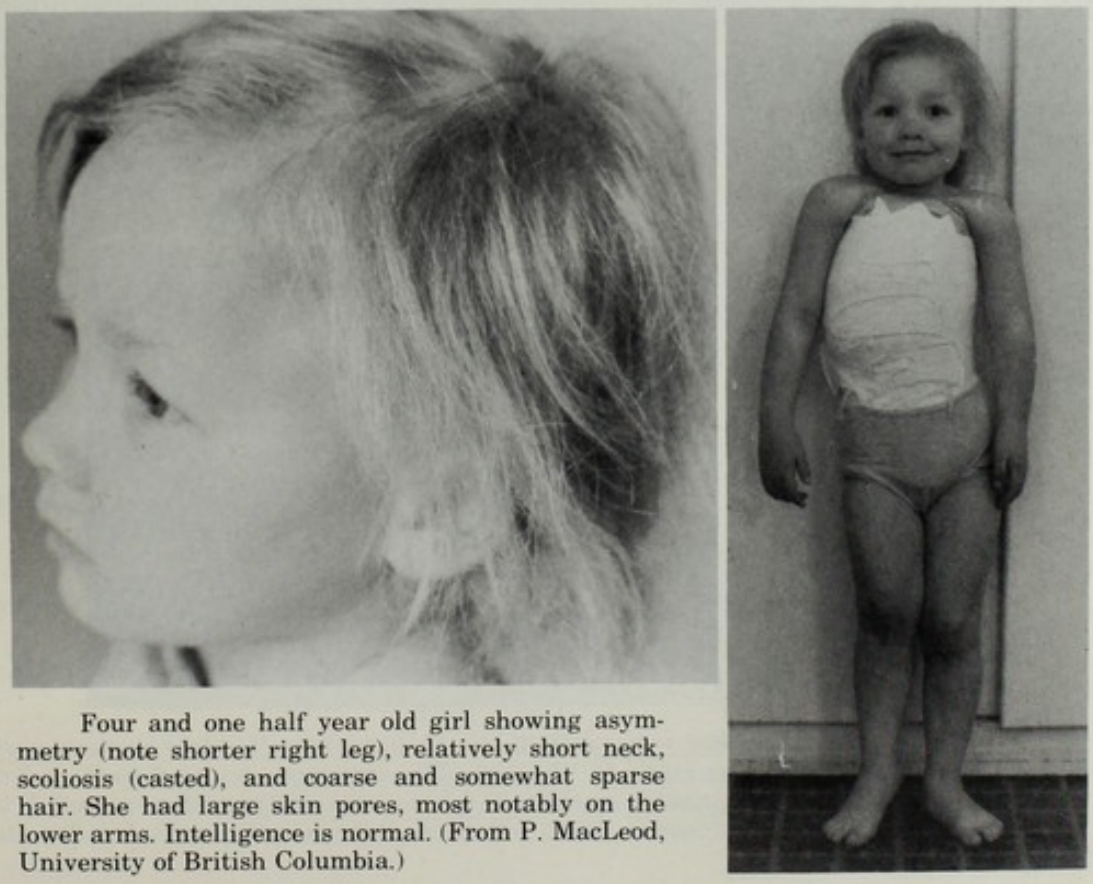
OCCASIONAL ABNORMALITIES. Cataracts (17 per cent), ichthyosiform skin (27 per cent), short neck. Hydramnios, hydrops. Mild to moderate mental deficiency.

NATURAL HISTORY. Failure to thrive and/or infection may occur in early infancy. If the patient survives the first few months the prognosis for survival is good. Orthopedic problems including scoliosis are frequent and there is an enhanced risk of cataract.

ETIOLOGY. Autosomal dominant with variance in expression. Many cases represent fresh gene mutations from unaffected parents.

REFERENCES

1. Conradi, E.: Vorzeitiges Auftreten von Knochenund eigenartigen Verkalkungskernen bei Chondrodystrophia foetalis hypoplastica. Jahrb. Kinderheilkd., *80*:86, 1914.
2. Hünermann, C.: Chondrodystrophia calcificans congenita als abortive Form der Chondrodystrophie. Z. Kinderheilkd., *51*:1, 1931.
3. Spranger, J., Opitz, J. M., and Bidder, U.: Heterogeneity of chondrodysplasia punctata. Humangenetik, *11*:190, 1971.



Four and one half year old girl showing asymmetry (note shorter right leg), relatively short neck, scoliosis (casted), and coarse and somewhat sparse hair. She had large skin pores, most notably on the lower arms. Intelligence is normal. (From P. MacLeod, University of British Columbia.)

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA SYNDROME

(Chondrodysplasia Punctata, Rhizomelic Type)

Short Humeri and Femurs, Coronal Cleft in Vertebrae, Punctate Epiphyseal Mineralization

Spranger, et al.[1, 2] clearly distinguished the rhizomelic (short proximal limb) type of chondrodysplasia punctata as a separable entity from the Conradi-Hünermann type of chondrodysplasia punctata. Besides the nine personal cases, Spranger, et al.[1, 2] were able to find 33 additional cases from the past literature.

ABNORMALITIES[1, 2]

Growth. Slow growth.

CNS. Mental deficiency, with or without spasticity, microcephaly.

Craniofacies. Low nasal bridge and flat facies with or without upward slanting palpebral fissures. Cataracts (72 per cent).

Limbs. Symmetrical proximal shortening, humeri and femurs. Metaphyseal splaying and cupping, especially at the knee, with sparse and irregular trabeculae. Epiphyseal and extraepiphyseal foci of calcification in early infancy with later epiphyseal irregularity. Multiple joint contractures.

Spine. Coronal cleft noted on lateral roentgenograms with dysplasia and irregularity of vertebrae.

Pelvis. Trapeziform dysplasia of upper ileum.

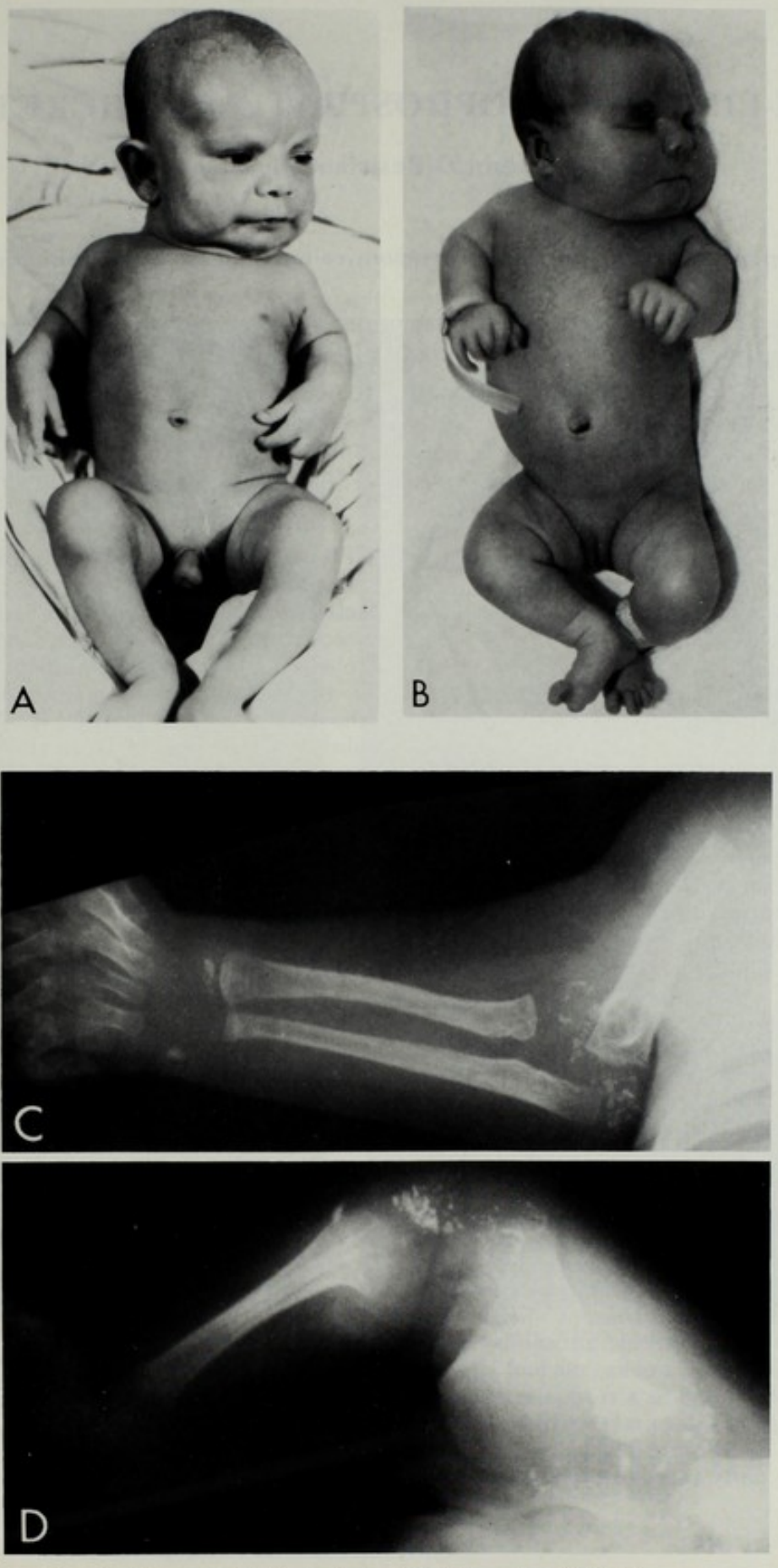
OCCASIONAL ABNORMALITIES. Ichthyosiform skin dysplasia (28 per cent).

NATURAL HISTORY. These patients usually have a severe problem in growth and mental development and die prior to one to two years of age. Only one case is known to have survived to the age of five years. No effective management is known. Punctate epiphyseal and nonepiphyseal mineralization, which is not specific to this disorder, may not be found in all cases, especially when the diagnosis is not made in early infancy.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Spranger, J. W., Bidder, U., and Voelz, C.: Chondrodysplasia punctata (Chondrodystrophia calcificans). II. Der rhizomele Type. Fortschr. Geb. Roentgenstr. Nuklearmed., *114*:327, 1971.
2. Spranger, J. W., Opitz, J. M., and Bidder, U.: Heterogeneity of chondrodysplasia punctata. Humangenetik, *11*:190, 1971.



A, Seven week old male. (From Ford, G. D., et. al.: Pediatrics, *8*:380, 1951.)
B, Young infant. Note the short upper arms. (Courtesy of J. M. Opitz and J. Spranger, University of Wisconsin.)
C and *D*, Roentgenograms of the arm and leg of an infant showing proximal shortening with aberrant form and punctate mineralization. (Courtesy of R. A. Hadley and G. Gibbs, University of Nebraska.)

X-LINKED HYPOPHOSPHATEMIC RICKETS

(Vitamin D-Resistant Rickets)

Hypophosphatemia, Rickets, Unresponsive to Usual Dosage of Vitamin D

ABNORMALITIES[1-3]

Growth. Mild to moderate growth deficiency. Adult stature 130 to 160 cm.

Metabolic. Hypophosphatemia with diminished renal tubular reabsorption of phosphorus, questionably diminished absorption of phosphorus and calcium from the gastrointestinal tract, and diminished rate of new bone formation. Roentgen evidence of rickets, unresponsive to physiological amounts of vitamin D.

Skeletal. Rickets. Bowing of lower limbs with weight bearing, slow growth, shortness of stature, waddling gait, coxa vara.

OCCASIONAL ABNORMALITIES

Dental.[2] Large pulp chamber with enamel hypoplasia.
Gingival and periapical infection.
Delayed eruption of dentition.

Skeletal. Craniosynostosis, dolichocephaly, scoliosis, pseudo-fractures, bony protuberances at the site of major muscle attachments in the adult.

NATURAL HISTORY. Harrison[3] has emphasized that growth is normal in early infancy until the serum phosphorus falls to low values around six months. Although large amounts of vitamin D can improve the X-ray appearance of the bone and limit the amount of deformity, the serum phosphorus usually remains subnormal and the patients continue to grow at a slow pace. The danger of vitamin D in large dosage is potentially a more harmful one than the untreated disease, and therefore such therapy should only be utilized when the serum calcium can be monitored every two to four weeks; normal growth should not be anticipated as a response. Possibly a moderate dosage of vitamin D with excess oral phosphate may be a more efficacious mode of management. A daily inorganic phosphate salt intake of 1 to 4 grams in 5 divided doses plus 10,000 to 50,000 units of vitamin D_2 per day has been effective in this regard. Deformities may progress into adult life; these include exostoses at the sites of muscle attachment, spinal fusion, and scoliosis.

ETIOLOGY. X-linked dominant in terms of hypophosphatemia with lesser severity in affected females.[1] DeLuca, et al.[4] administered tritiated vitamin D_3 to two patients and two controls and found a longer half-life of the tritiated D_3 in the hypophosphatemic rickets patients, who had a 20-fold greater amount of aqueous soluble metabolites of D_3 in the serum than did the controls. These data, although inconclusive, suggest an abnormality in degradation of vitamin D in this disorder.

REFERENCES

1. Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., and Burnett, C. H.: A genetic study of familial hypophosphatemia and vitamin D resistant rickets with a review of the literature. Medicine, *37*:97, 1958.
2. Archard, H. O., and Witkop, C. J.: Hereditary hypophosphatemia (vitamin D-resistant rickets) presenting primary dental manifestations. Oral Surg., *22*:184, 1966.
3. Harrison, H. E., Harrison, H. C., Lifshitz, F., and Johnson, A. D.: Growth disturbance in hereditary hypophosphatemia. Am. J. Dis. Child., *112*:290, 1966.
4. DeLuca, H. F., Lund, J., Rosenbloom, A., and Lobeck, C. C.: Metabolism of tritiated vitamin D_3 in familial vitamin D-resistant rickets with hypophosphatemia. J. Pediatr., *70*:828, 1967.
5. Glorieux, F. H., Scriver, C. R., Reade, T. M., Goldman, H., and Roseborough, A.: Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. N. Engl. J. Med., *287*:481, 1972.



Seven year old with height age of four and one half years. Serum phosphorus, 2.2 mg per 100 ml.

PSEUDO-VITAMIN D DEFICIENCY RICKETS

Rickets, Hypotonia, Hypocalcemia, Unresponsive to Usual Dosage of Vitamin D

Prader, et al.[1] described this disorder in 1961 and increasing recognition has resulted in about 40 cases being reported.

ABNORMALITIES[1-4]

General. Growth deficiency, hypotonia, slow motor progress, +/− seizures (tetany).

Skeletal. Rickets, +/− fractures, large fontanels.

Dental. Enamel hypoplasia, postnatal onset.

Metabolic. Hypocalcemia, elevated serum alkaline phosphatase, +/− mild to moderate hypophosphatemia, hyperaminoaciduria, and mild renal tubular acidosis.

NATURAL HISTORY AND THERAPY. The natural history is highly comparable to that of severe early infantile vitamin D deficiency rickets with onset in the first six to nine months of hypotonia, growth deficiency, skeletal evidences of rickets, plus or minus signs of hypocalcemia, such as seizures. These patients are not responsive to vitamin D in usual dosage, but large amounts of the vitamin will bring about a complete return to normal, including catch-up growth. The initial dosage of vitamin D has been 50,000 to 300,000 units per day and the maintenance dosage has varied from 20,000 to 150,000 units, most commonly being 30,000 to 40,000 units per day.

This disorder differs from X-linked hypophosphatemic rickets by virtue of having an earlier onset with hypotonia, more severe hypocalcemia, less severe hypophosphatemia, and complete clinical and laboratory restitution on relatively high dosage of vitamin D.

ETIOLOGY. Autosomal recessive, with a question of autosomal dominant inheritance in some families.[1] These findings suggest possible genetic heterogeneity for this clinical disorder.

Impaired intestinal absorption of calcium has been noted in one case[4] and the question has been raised of there being a metabolic problem in the hydroxylation of vitamin D_2 (cholecalciferol) to the biologically active form, 25-hydroxy cholecalciferol.[3]

REFERENCES

1. Prader, A., Illig, R., and Heierli, E.: Eine besondere Form der primären vitamin-D-resistenten Rachitis mit Hypocalcämie und autosomal-dominantem Erbgana: die hereditäre Pseudo-Mangelrachitis. Helv. Paediatr. Acta, *16*:452, 1961.
2. Stoop, J. W., Schraagen, M. J. C., and Tiddens, H. A. W. M.: Pseudo vitamin D deficiency rickets. Report of four new cases. Acta Paediatr. Scand., *56*:607, 1967.
3. Fanconi, A., and Prader, A.: Die hereditäre Pseudomangelrachitis. Helv. Paediatr. Acta, *24*:423, 1969.
4. Hamilton, R., Harrison, J., Fraser, D., Radde, I., Morecki, R., and Paunier, L.: The small intestine in Vitamin D dependent rickets. Pediatrics, *45*:364, 1970.

KENNY SYNDROME

Short Stature, Slim Medullary Cavity, Transient Hypocalcemia, Myopia

Kenny and Linarelli[1] recently described this entity in a mother and her son.

ABNORMALITIES

Growth. Short stature of prenatal onset; the affected woman was 48 inches tall.

Skeleton. Inner cortical thickening of bone with slim medullary cavities.

Late ossification of anterior fontanel.

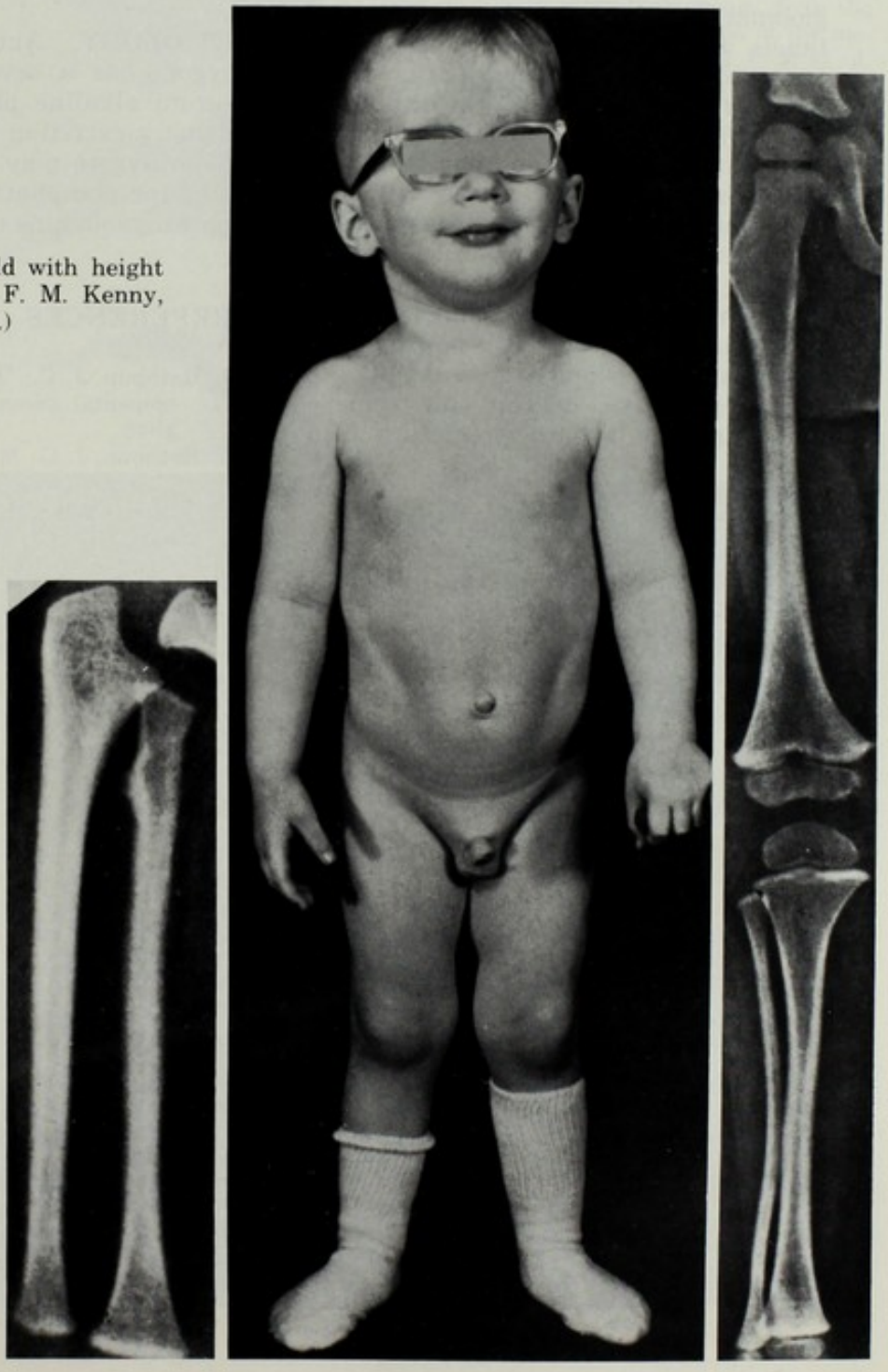
Eye. Myopia.

Metabolic. Transient hypocalcemia during early infancy in the boy and following surgery in his mother.

ETIOLOGY. Presumed autosomal dominant.

REFERENCES

1. Kenny, F. M., and Linarelli, L.: Dwarfism and cortical thickening of tubular bones. Am. J. Dis. Child., *111*:201, 1966.
2. Caffey, J.: Congenital stenosis of medullary spaces in tubular bones and calvaria in two proportionate dwarfs, mother and son, coupled with transitory hypocalcemic tetany. Am. J. Roentgenol. Radium Ther. Nucl. Med., *100*:1, 1967.



Three and one half year old with height age of 16 months. (Courtesy of F. M. Kenny, Children's Hospital of Pittsburgh.)

HYPOPHOSPHATASIA SYNDROME

Bowlegs with Irregular Metaphyseal Rarefaction, Early Loss of Deciduous Teeth, Late Closure of Fontanels with or without Craniosynostosis

Rathbun[1] recognized this disease in 1948, and numerous cases have been documented subsequently.

ABNORMALITIES. There is wide variance in severity.

Growth. Deficiency, variable in degree.

Cranium. Variance from poorly mineralized globular cranium to late closure of wide fontanels with tendency toward craniosynostosis and increased intracranial pressure.

Other Skeletal. Varying features include hypoplastic fragile bone of varying density with irregular lack of metaphyseal mineralization, bowed lower extremities with overlying cutaneous dimpling, and short ribs with rachitic rosary and small thoracic cage. Less severely affected patients may have irregular, rachitic appearing incomplete metaphyseal mineralization, with bowing of the lower extremities and awkward gait.

Dentition. Defective dentin and cementum with tendency toward premature loss of teeth.

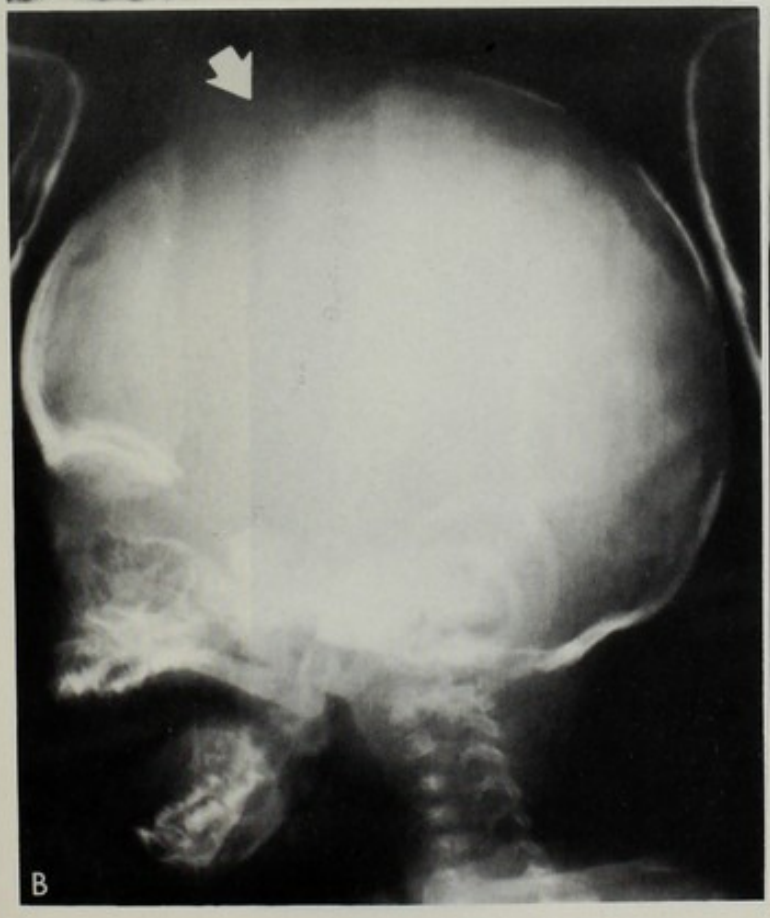
NATURAL HISTORY. Those patients who have the severe type of prenatal defect generally die of respiratory insufficiency during early infancy. Patients with moderately severe cases tend to have early failure to thrive, hypotonia, irritability and occasionally seizures, anemia and/or hypercalcemia, and nephrocalcinosis. The hypercalcemia may be responsive to hydrocortisone analogue therapy. About 50 per cent of the patients die in early infancy. The survivors and those who are more mildly affected may have bone pain, dental problems, and occasionally a fracture; but the osseous abnormalities tend toward improvement with time.

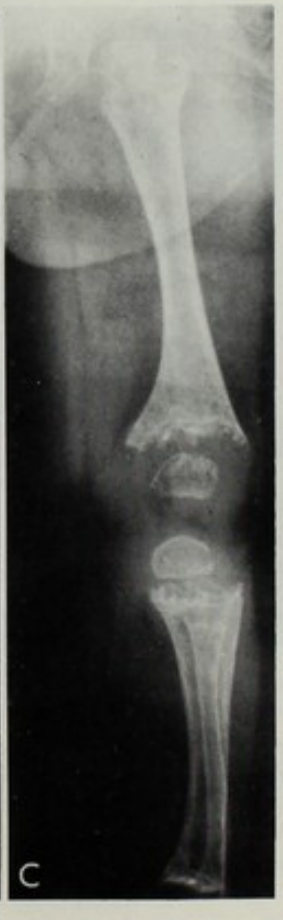
ETIOLOGY. Autosomal recessive. The homozygote has a severe deficiency of tissue and serum alkaline phosphatase and an excessive urinary excretion of phosphoethanolamine. The heterozygote may have a low value for serum alkaline phosphatase and mildly elevated phosphoethanolamine excretion.

REFERENCES

1. Rathbun, J. C.: "Hypophosphatasia." A new developmental anomaly. Am. J. Dis. Child., *75*:822, 1948.
2. Rathbun, J. C., MacDonald, J. W., Robinson, H. M. C., and Wanklin, J. M.: Hypophosphatasia: a genetic study. Arch. Dis. Child., *36*:540, 1961.
3. Kellsey, D. C.: Hypophosphatasia and congenital bowing of the long bones. J.A.M.A., *179*:187, 1962.
4. MacPherson, R. I., Kroeker, M., and Houston, C. S.: Hypophosphatasia. J. Can Assoc. Radiol., *23*:16, 1972.









A to C, Moderately affected 11 month old who had complete craniosynostosis. Though her skull x-ray at six months showed incomplete mineralization, the sutures were fused with a bulging anterior fontanel *(arrow).* Her long bones at 11 months showed poor mineralization with rachitic changes.

D, Lower limb roentgenogram of one day old severely affected patient who died at three days with thrombocytopenia. Note the incomplete ragged mineralization at the metaphyses. (From MacPherson, R. I., et al.: J. Can Assoc. Radiol., *23*:16, 1972.)

HYPERPHOSPHATASIA-OSTEOECTASIA SYNDROME

Macrocranium, Diaphyseal Widening, Hyperphosphatasia

Studies on two siblings with this disorder were reported initially in 1966 through 1968[1,2] and at least one other description of affected siblings has been recorded. The basic problem leads to rapid turnover of lamellar bone with broadening of diaphyses and calvarium, extremely thin cortices, weak bone, and linear growth deficiency.

ABNORMALITIES[1,2]

Growth. Growth deficiency.

Skeletal. Broadened diaphyses, bowing, fixation of elbows. Thickened cranium with prominent frontal and mastoid areas. Osteoporosis with pectus carinatum and flared ribs, biconcave vertebrae and kyphoscoliosis, and femoral heads indenting into pelvis.

Metabolic. Elevated serum alkaline and acid phosphatase and five to ten times elevated urine leucine amino acid peptidase and uric acid, presumably secondary to rapid turnover of bone.

Other. Bluish sclerae. Carious teeth.

NATURAL HISTORY. Becoming evident during the first year, there is progressive macrocranium, bowing, growth deficiency, and occasional fractures. The cranial thickening may lead to nerve compression and deafness. Intelligence is usually normal and they have been cheerful with limited discomfort. Surgical correction of the limb bowing has apparently been of some value.

ETIOLOGY. Presumed autosomal recessive.

REFERENCES

1. Eyring, E. J., and Eisenberg, E.: Congenital hyperphosphatasia. A clinical, pathological, and biochemical study of two cases. J. Bone Joint Surg. [Am.], *50*:1099, 1968.
2. Thompson, R. C., Jr., Gaull, G. E., Horwitz, S. J., and Schenk, R. K.: Hereditary hyperphosphatasia. Studies of three siblings. Am. J. Med., *47*:209, 1969.





The same affected siblings as in the original reports[1] at a later age. (Courtesy of S. Bintliff, Kauikeolani Children's Hospital, Honolulu.)

HAJDU-CHENEY SYNDROME

(Cheney Syndrome, Acro-Osteolysis Syndrome, Arthro-Dento-Osteo Dysplasia)

Early Loss of Teeth, Acro-Osteolysis, Lax Joints

Originally described by Hajdu and Kauntze[1] in 1948, and more extensively reported by Cheney,[2] the features of this disorder in 13 patients were summarized by Herrmann, et al.[3] The basic defect appears to be of connective tissue, most strikingly affecting the development and persistence of skeletal tissues.

ABNORMALITIES

Growth. Small stature, augmented by osseous compression.

Cranium. Wormian bones, failure of ossification of sutures, absence of frontal sinus, elongated sella torsica, development of basilar impression and bathrocephaly.

Mandible. Small with diminished ramus.

Dentition. Resorption of alveolar process with early loss of teeth.

Spine. Biconcave vertebrae, kyphoscoliosis.

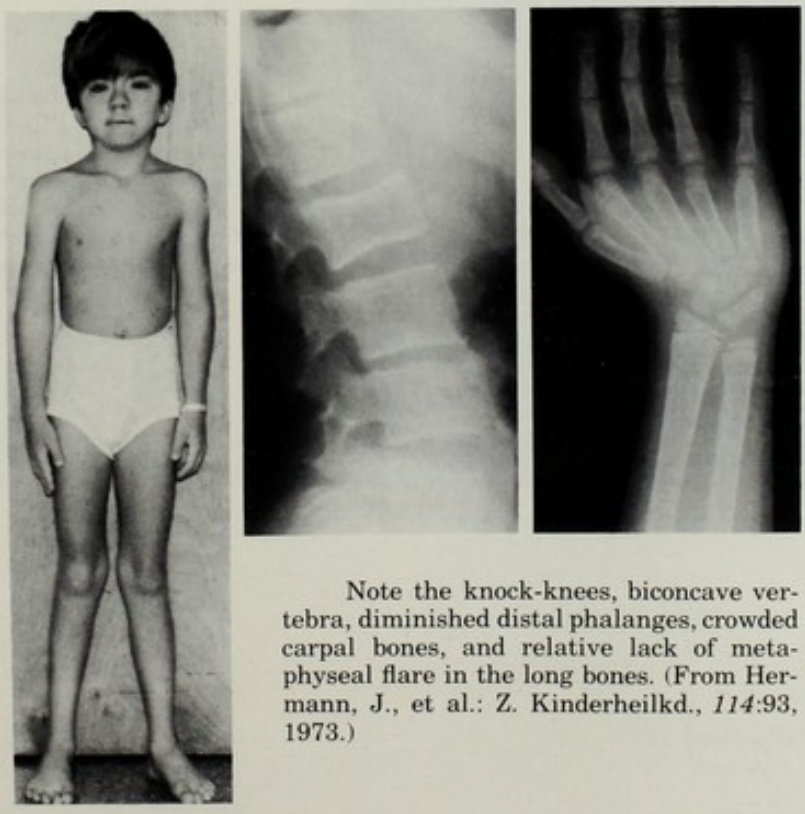
Limbs. Short distal digits and nails with acro-osteolysis. Crowded carpal bones. Joint laxity.

NATURAL HISTORY. Though the diagnosis is seldom made in childhood, the onset of the disorder is usually during childhood, as indicated by the hand changes. Pain is a frequent manifestation, especially in the hands, the patients are often weak, and pathological fractures are liable to occur. Osseous compression may actually result in a decrease in stature and the basilar compression can be life threatening.

ETIOLOGY. Autosomal dominant, with sporadic cases presumably representing fresh gene mutation.

REFERENCES

1. Hajdu, N., and Kauntze, R.: Cranio-skeletal dysplasia. Br. J. Radiol., *21*:42, 1948.
2. Cheney, W. D.: Acro-osteolysis. Amer. J. Roentgenol. Radium Ther. Nucl. Med., *94*:595, 1965.
3. Herrmann, J., Zugive, F. T., Gilbert, E. F., and Opitz, J. M.: Arthro-Dento-Osteo-Dysplasia (Hajdu-Cheney syndrome). Review of a genetic "Acro-Osteolysis" syndrome. Z. Kinderheilkd., *114*:93, 1973.



Note the knock-knees, biconcave vertebra, diminished distal phalanges, crowded carpal bones, and relative lack of metaphyseal flare in the long bones. (From Hermann, J., et al.: Z. Kinderheilkd., *114*:93, 1973.)

GORLIN FRONTO-METAPHYSEAL DYSPLASIA SYNDROME

Prominent Supraorbital Ridges, Joint Limitations, Splayed Metaphyses

Only a few sporadic cases of this disorder have been recognized since Gorlin and Cohen's initial report[1] in 1969.

ABNORMALITIES[1, 2]

Craniofacial. Coarse facies with wide nasal bridge and prominent supraorbital ridges. Incomplete sinus development. Partial anodontia. High palate. Small mandible with decreased angle and prominent antigonial notch.

Limbs. Partial ankylosis in fingers, wrist, elbow, knee, ankle. Arachnodactyly with long, poorly modeled metacarpal and proximal and midphalangeal bones. Splayed Erlenmeyer-flask metaphyses of femur, tibia. Partial fusion of carpal and of tarsal bones.

Other Skeletal. Wide foramen magnum and wide interpedicular distance of vertebrae. Flared pelvis.

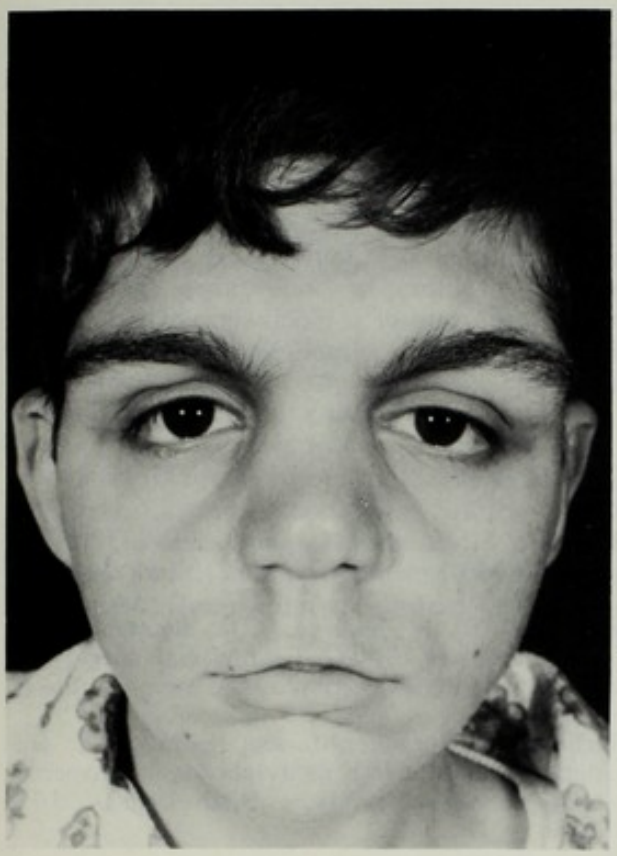
Other. Cardiac murmur, cause unknown. Deafness, conductive. Cryptorchidism. Hirsutism.

NATURAL HISTORY. Predominantly a dysplasia of teeth, bone, and connective tissue, there may be some progression in disability with time, including osteolysis in carpal and tarsal bones.

ETIOLOGY. Unknown. All cases sporadic.

REFERENCES

1. Gorlin, R. J., and Cohen, M. M.: Frontometaphyseal dysplasia: a new syndrome. Am. J. Dis. Child., *118*:487, 1969.
2. Danks, D. M., Mayne, V., Hall, R. K., and McKinnon, M. C.: Fronto-metaphyseal dysplasia. A progressive disease of bone and connective tissue. Am. J. Dis. Child., *123*:254, 1972.







Eleven year old. Note broad prominent nasal bridge and thickened tissues with prominent philtrum. The skull shows supraorbital bossing with small paranasal sinuses. Note the bowing of the fibula and metaphyseal flaring of tibia; long, poorly modeled tubular bones of hand, and partial lysis of carpal bones. (From Danks, D. M., et al.: Am. J. Dis. Child., *123*:254, 1972.)

CRANIOMETAPHYSEAL DYSPLASIA SYNDROME

Bony Wedge over Bridge of Nose, Mild Splaying of Metaphyses

Often confused with the Pyle metaphyseal dysplasia syndrome, this disorder has more profound craniofacial hyperostosis and less metaphyseal broadening than in Pyle's disease.

ABNORMALITIES

Craniofacial. Thick, with dense base, cranial vault, facial bones, and mandible. Variable absence of pneumatization.

Unusual thick bony wedge over bridge of nose and supraorbital area with hypertelorism and relatively small nose. Variable proptosis of eyes.

Compression of foramina with cranial nerve deficits, headache, and narrow nasal passages with rhinitis.

Limbs. Mild to moderate metaphyseal broadening with diaphyseal sclerosis.

NATURAL HISTORY. The disease is evident from infancy, and these individuals may have serious problems from compression of the brain and cranial nerves and deafness. They are of normal intelligence. The autosomal recessive type is more severe and may result in facial paralysis and loss of vision.

ETIOLOGY. Both an autosomal dominant and a presumed autosomal recessive type have been delineated, the latter being more severe in degree. The problem in bone morphogenesis is thought to be one of osteoclasis, with defective reabsorption and remodeling of secondary spongiosa.

REFERENCES

1. Spranger, J., Paulsen, K., and Lehmann, W.: Die kraniometaphysare Dysplasie. Z. Kinderheilkhd., *93*:64, 1965.
2. Millard, D. R., Jr., Maisels, D. O., Batstone, J. H. F., and Yates, B. W.: Craniofacial surgery in craniometaphyseal dysplasia. Am. J. Surg., *113*:615, 1967.
3. Gorlin, R. J., Spranger, J., and Koszalka, M.: Genetic craniotubular bone dysplasias and hyperostoses. A critical analysis. Birth Defects, *5*:79, 1969.



Eleven year old girl with the autosomal dominant type. The hyperostosis is already causing the fullness noted in the area of the nasal bridge. Hearing loss began at age nine years. The long bones show the Erlenmeyer-flask shape at the metaphyseal area. (Courtesy of D. L. Rimoin, Harbor General Hospital, Torrance, California.)

PYLE METAPHYSEAL DYSPLASIA SYNDROME

(Pyle's Disease)

Marked Splaying Metaphyses, Mild Supraorbital Hyperplasia

Described in 1931 by Pyle, this disorder was more fully characterized and distinguished from craniometaphyseal dysplasia by Gorlin, et al.[2] in 1970. More than 17 cases have been recognized.

ABNORMALITIES

Craniofacial. Mild supraorbital hyperplasia and thickening of calvarium.

Limbs. Marked Erlenmeyer-flask-like flare of distal femur and proximal tibia with cortical thinning and osteoporosis. Similar but less striking changes in other distal long bones plus distal metacarpals and proximal phalanges. Genu valgus. Limited elbow extension.

Other Skeletal. Thickening of ribs, pubic, ischial, and proximal clavicle.

OCCASIONAL ABNORMALITIES. Muscle weakness, joint pain, scoliosis, fractures.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Pyle, E.: A case of unusual bone development. J. Bone Joint Surg. [Am.], *13*:874, 1931.
2. Gorlin, R. J., Koszalka, M. F., and Spranger, J.: Pyle's disease (familial metaphyseal dysplasia). J. Bone Joint Surg. [Am.], *52*:347, 1970.

ALBERS-SCHÖNBERG SYNDROME

(Severe Osteopetrosis)

Dense, Thick, Fragile Bone, Secondary Pancytopenia, Cranial Nerve Compression

More than 50 cases of this lethal disorder have been reported since the initial description by Albers-Schönberg[1] in 1907.

ABNORMALITIES

Skeleton. Thick, dense fragile bone with modeling alterations such as obtuse mandibular angle, partial aplasia of distal phalanges, straight femora, blocky "bone within a bone" metacarpals, and macrocephaly with frontal bossing. Marrow compression leads to pancytopenia, and compression of cranial foramina may lead to cranial nerve palsies, blindness, and/or hydrocephalus.

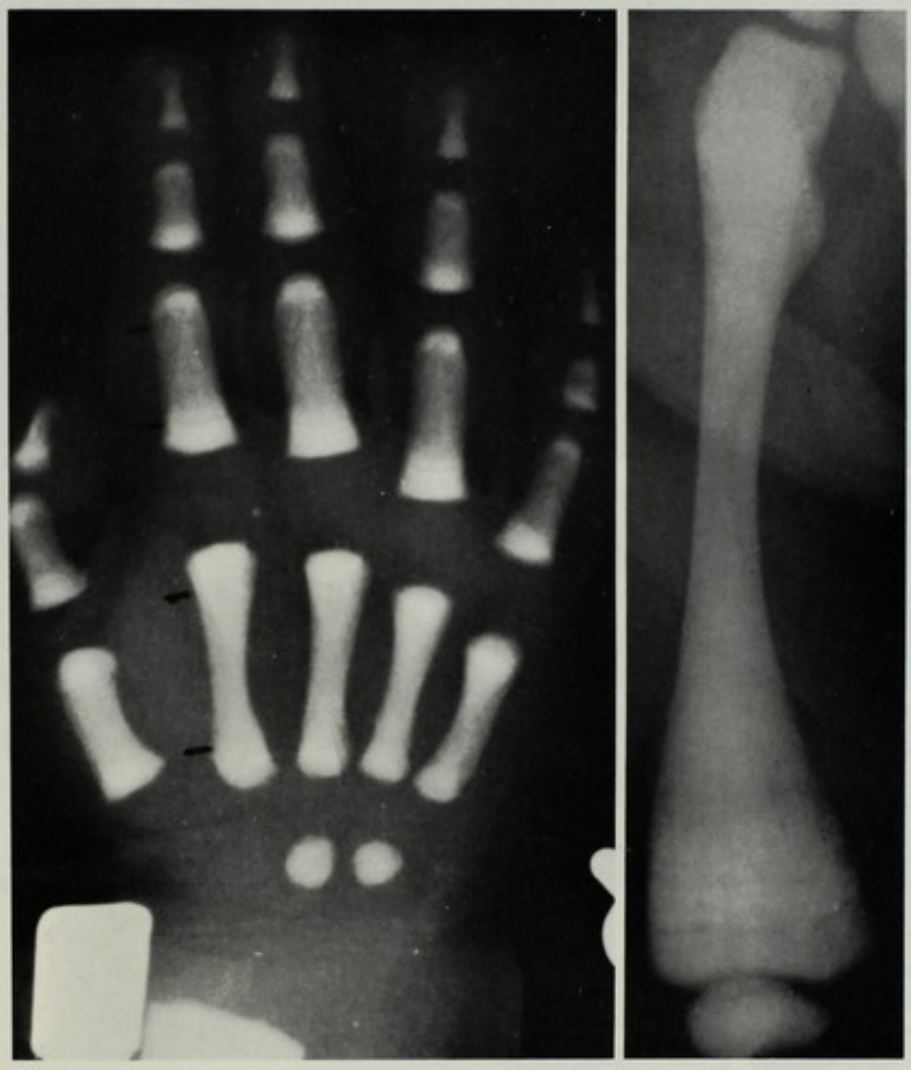
Metabolic. Serum calcium may be low and serum phosphorus elevated.

NATURAL HISTORY. Usually evident at birth with subsequent severe complications and death in infancy or early childhood.

ETIOLOGY. Autosomal recessive. There appears to be defective reabsorption of immature bone. The question has been raised as to whether this disease may represent an abnormality in thyrocalcitonin metabolism, a question which merits close study.

REFERENCES

1. Albers-Schönberg, H.: Eine bisher nicht beschriebene Allgemeinekrankung des Skelettes im Röntgenbilde. Fortschr. Geb. Roentgenstr. Nuklearmed., *11*:261, 1907.
2. Tips, R. L., and Lynch, H. T.: Malignant congenital osteopetrosis resulting from a consanguineous marriage. Acta Paediatr. Scand., *51*:585, 1962.



Eight month old. The sclerotic skeleton shows the "bone within a bone" (endobone) appearance, vertical striations at the metaphyseal-diaphyseal juncture, and broad metaphyses.

MAROTEAUX-LAMY PYKNODYSOSTOSIS SYNDROME

Osteosclerosis, Short Distal Phalanges, Delayed Closure of Fontanels

Though cleidocranial dysostosis associated with osteosclerosis and bone fragility had been recognized prior to 1962,[1] this condition was not well clarified until Maroteaux and Lamy[2] described it under the eponym of pyknodysostosis (pyknos = dense).

ABNORMALITIES

Growth. Small stature.

Skeletal. Osteosclerosis with tendency toward transverse fracture.

Craniofacial. Frontal and occipital prominence, delayed closure of sutures, persistence of anterior fontanel, wormian bones, lack of frontal sinus. Facial hypoplasia with prominent nose and narrow grooved palate. Obtuse angle to mandible, which may be small.

Teeth. Irregular permanent teeth with or without partial anodontia, delayed eruption, carious teeth.

Clavicle. Dysplasia to loss of acromion end.

Digits. Acro-osteolytic dysplasia of distal phalanges, especially of index finger. Wrinkled skin over dorsum of distal fingers. Flattened and grooved nails.

OCCASIONAL ABNORMALITIES. Mental retardation (six of 32). Scoliosis.

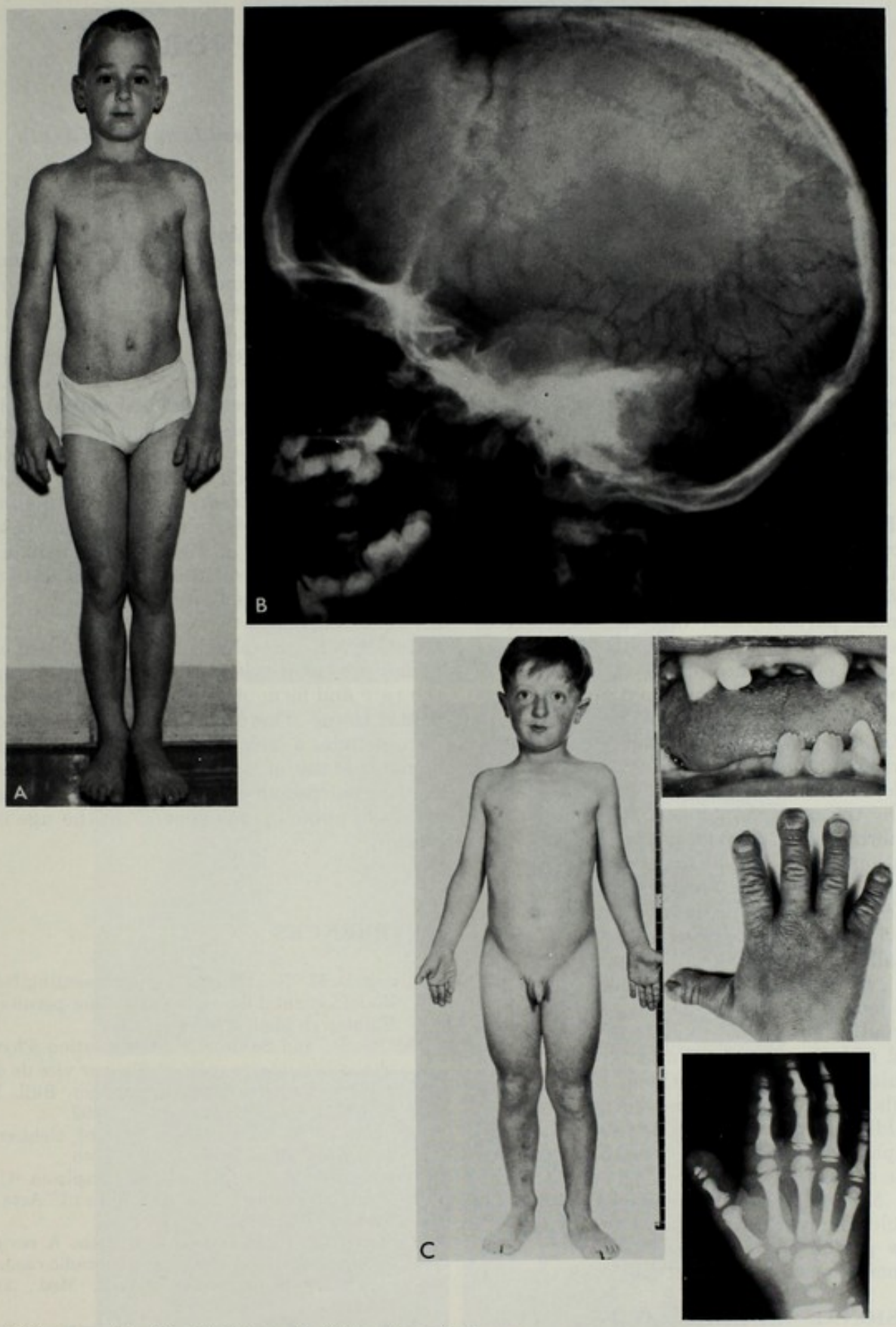
NATURAL HISTORY. About two thirds of the patients have had fractures, most commonly in the lower extremity, including metatarsals, mandible, and clavicle. There may be a progressive loss in the distal phalanges and outer clavicle and persistent open fontanels, especially the posterior. Special dental care is often indicated.

ETIOLOGY. Consanguinity in seven of 32 families[4] and sibship occurrence from unaffected parents are indicative of an autosomal recessive determination. However, Shuler[3] discovered the syndrome in a maternal uncle of an affected male and therefore raised the question of X-linked recessive in that family.

COMMENT. The painter Toulouse-Lautrec is considered to have had pyknodysostosis.

REFERENCES

1. Thomsen, G., and Guttadauro, M.: Cleidocranial dysostosis associated with osteosclerosis and bone fragility. Acta Radiol., *37*:559, 1952.
2. Maroteaux, P., and Lamy, M.: La pycnodysostose. Presse Med., *70*:999, 1962.
3. Shuler, S. E.: Pycnodysostosis. Arch. Dis. Child., *38*:620, 1963.
4. Elmore, S. M.: Pycnodysostosis: a review. J. Bone Joint Surg. [Am.], *49-A*:153, 1967.



A, Ten year old with height age of eight and one half years.

B, Patient shown in *A*. Note the open fontanel and lambdoid suture, absence of frontal sinus or mastoid air cells, obtuse angle of mandible, and delay in eruption of permanent dentition.

C, Seven and one half year old with height age of four and one half years. Note the generally dense bone and partial loss of several distal phalanges. (From Shuler, S. E.: Arch. Dis. Child., *38*:620, 1963.)

CLEIDOCRANIAL DYSOSTOSIS SYNDROME

Defect of Clavicle, Late Ossification of Cranial Sutures, Delayed Eruption of Teeth

A possible example of this rather generalized dysplasia of osseous and dental tissues was detected in the skull of a Neanderthal man.[1] The more obvious features of the defect in clavicle and cranium prompted Marie and Sainton[2] to utilize the term cleidocranial dysostosis for this condition; however, the more generalized dysplasia of bone and teeth has been emphasized, and the term cleidocranial dysostosis only depicts a portion of the abnormal development. Well over 500 cases have been reported.

ABNORMALITIES. The following are frequent but not constant features:

Growth. Mild to moderate shortness of stature.

Craniofacial. Brachycephaly with bossing of frontal, parietal, and occipital bones; late closure of fontanels and mineralization of sutures; late or incomplete development of accessory sinuses and mastoid air cells; wormian bones; small sphenoid bones.

Mid-facial hypoplasia with low nasal bridge, narrow high-arched palate.

Dentition. Late eruption of dentition, especially the permanent teeth, which are often abnormal with aplasia, malformed roots, retention cysts, enamel hypoplasia, enhanced caries, and supernumerary teeth.

Clavicle and Chest. Partial to complete aplasia of clavicle with associated muscle defects, small thorax with short oblique ribs.

Hands. Hand anomalies including asymmetrical length of fingers with long second metacarpal, short middle phalanges of second and fifth fingers, short and tapering distal phalanges with or without downcurving nails, cone-shaped phalangeal epiphyses in childhood, accessory proximal metacarpal epiphyses which fuse in childhood, and slow rate of carpal ossification.

Other Skeletal. Delayed mineralization of pubic bone with wide symphysis pubis, narrow pelvis, broad femoral head with short femoral neck, with or without coxa vara.

OCCASIONAL ABNORMALITIES. Cervical rib, small scapulae, scoliosis, kyphosis, flat acetabulae, osteosclerosis, increased bone fragility, deafness, cleft palate.

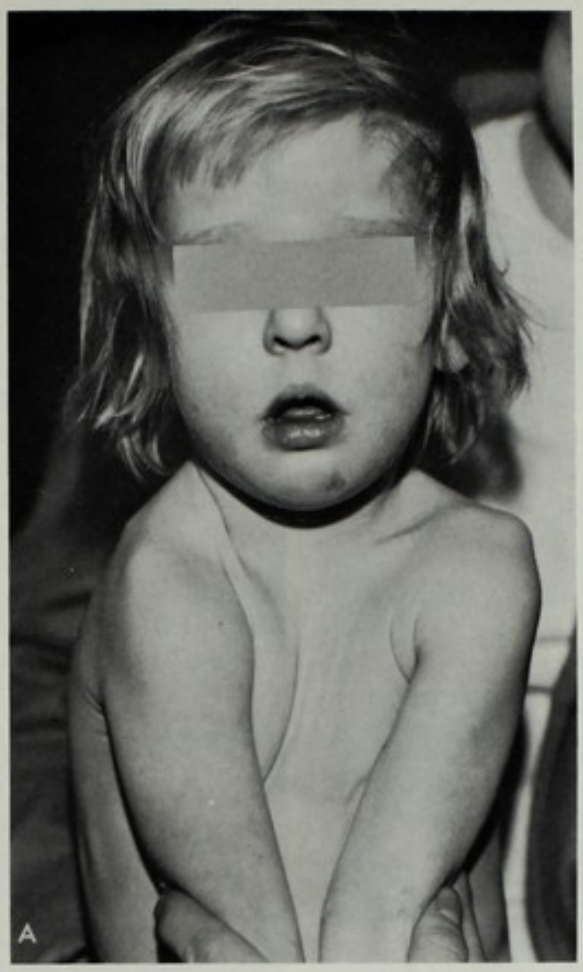
ETIOLOGY. Autosomal dominant with wide variability in expression, but usually showing penetrance. About one third of the cases represent fresh mutations.

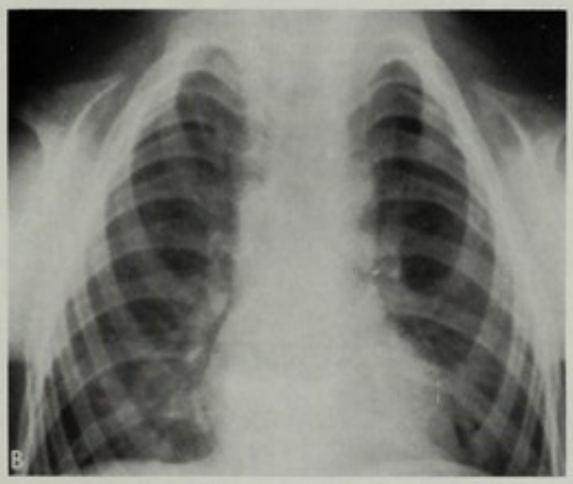
NATURAL HISTORY. Though stature is often reduced, mentality is usually normal. Hearing should be assessed and dental problems should be anticipated. Removal of deciduous teeth does not seem to hasten the eruption of permanent teeth, and the permanent teeth may be difficult to extract because of malformed roots. Narrow pelvis may necessitate cesarian section for delivery of the pregnant female with this condition. Narrow thorax may lead to respiratory distress in early infancy.

COMMENT. Emphasis should be placed on the rather generalized effect of this mutant gene on the rate and form of development of osseous and dental tissue. The degree of variance in expression includes a lack of defective clavicular development. Many of the radiological signs such as metacarpal pseudoepiphyses and late mineralization of pubic ramus depend on the age of the patient.

REFERENCES

1. Grieg, D. M.: Neanderthal skull presenting features of cleidocranial dysostosis and other peculiarities. Edinburgh Med. J., *40*:407, 1933.
2. Marie, P., and Sainton, P.: Observation d'hydrocephalie héréditaire (père et fils) par vice de developpement du crane et du cerveau. Bull. Mem. Soc. Med. Hop. (Paris), *14*:706, 1897.
3. Lasker, G. W.: The inheritance of cleidocranial dysostosis. Hum. Biol., *18*:103, 1946.
4. Jackson, W. P. U.: Osteo-dental dysplasia (Cleidocranial dysostosis). The "Arnold head." Acta Med. Scand., *139*:292, 1951.
5. Forland, M.: Cleidocranial dysostosis. A review of the syndrome and report of a sporadic case, with hereditary transmission. Am. J. Med., *33*:792, 1962.
6. Fauré, C., and Maroteaux, P.: Cleidocranial dysplasia. *In* Progress in Pediatric Radiology, Vol. 4, edited by H. J. Kaufmann. Basel, Karger, 1973, pp. 211–238.











Seven years old

A, Three and one half year old; height age, two and one half years. (From Smith, D. W.: J. Pediatr., *70*:500, 1967.)

B, Absent clavicles.

C, Poorly mineralized cranial sutures.

D, Hypoplasia of ilia, wide-spread pubic rami.

E, Mandible showing delay in eruption of permanent teeth.

(*C* and *E* courtesy of R. Scherz, Madigan General Hospital, Washington.)

STANESCO DYSOSTOSIS SYNDROME

Thick Cortical Bone, Brachycephalic Thin Skull, Relatively Short Upper Arm, Proportionately Short Fingers

Stanesco, et al.[1] studied seven of 11 affected individuals in three generations of one family and reported this condition in 1963. There are similarities to the Maroteaux and Lamy pyknodysostosis syndrome.

ABNORMALITIES. Based on seven cases.[1]

Growth. Small stature.

Craniofacial and Dental. Brachycephalic thin skull, often with depressions at frontoparietal sutures.

Lack of pneumatization in frontal and sphenoid bone. Shallow orbits with prominent eyes. Narrow maxilla. Small mandible with obtuse angle. Crowded teeth, sometimes small; enamel hypoplasia.

Long Bones. Dense with thick cortices. Relative shortness, especially of upper arm and hand.

OCCASIONAL ABNORMALITIES. Flattened roof of palate, sacralization of S-1, exostoses, fractures.

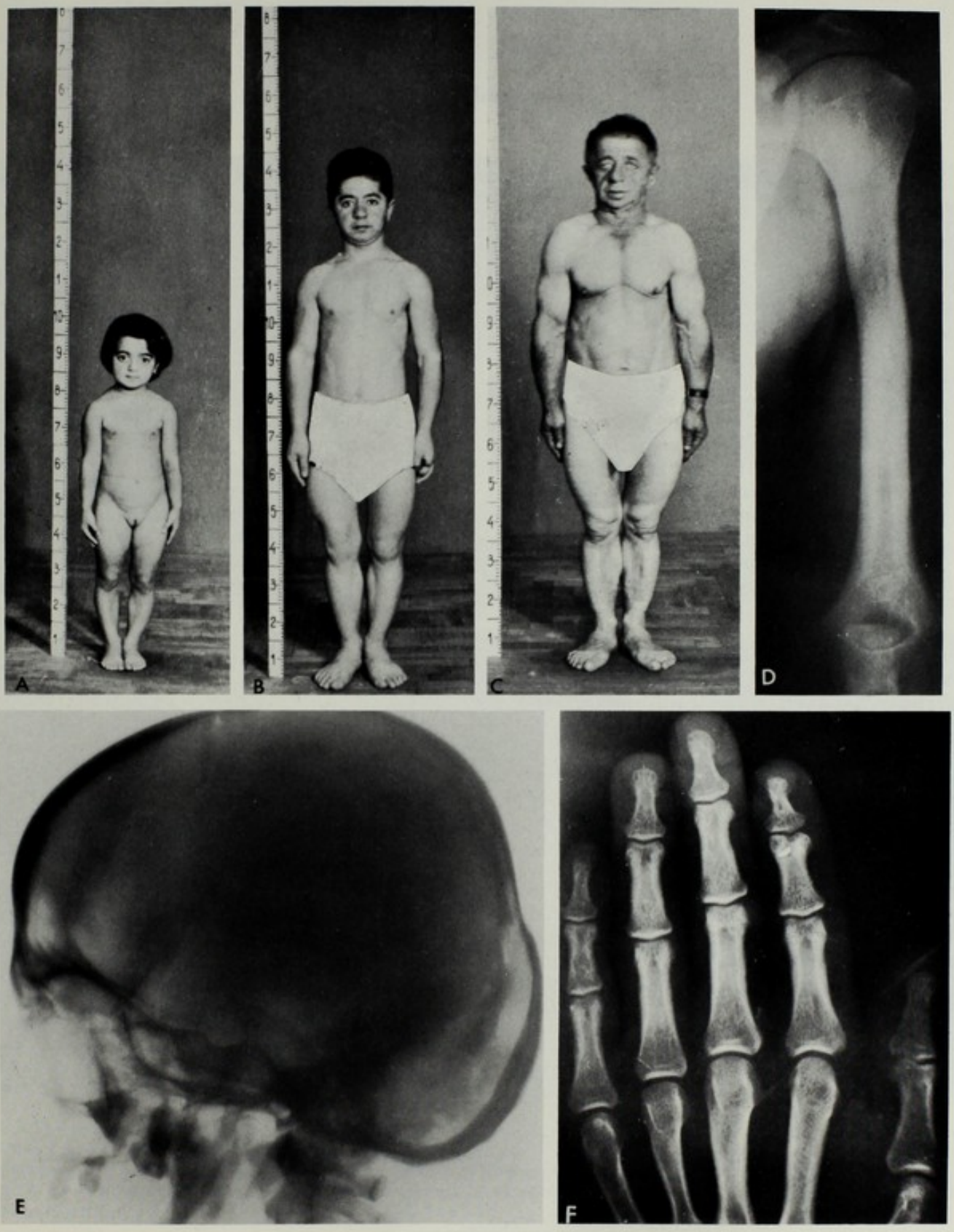
NATURAL HISTORY. These individuals have been of normal intelligence, with no problems in sexual development or reproduction. The bone tends to become more dense with age. Only one of the 11 affected members of the family was known to have had a fracture.

ETIOLOGY. Autosomal dominant with almost complete expression in all affected individuals.

COMMENT. The lack of defect in the distal phalanges in this disorder appears to be one of the easiest clinical points in distinguishing this disease from the type of pyknodysostosis described by Maroteaux and Lamy.

REFERENCE

1. Stanesco, V., Maximilian, C., Poenaru, S., Florea, I., Stanesco, R., Ionesco, V., and Ioanitiu, D.: Syndrome hereditaire dominant, etc. Rev. Fr. Endocrinol. Clin., *4*:219, 1963.



A to *C: A*, Nine year old; height age three years. *B*, Sixteen year old; height age, 10 years. *C*, Adult with height of 4 feet, 7 inches.

D, Humerus, showing thick, dense cortices.

E, Adult cranium, relatively dense with shallow sella and obtuse mandibular angle.

F, Adult hand showing minor alterations, but no osteolysis of distal phalanges, as found in pyknodysostosis. (From Stanesco, V., et al.: Rev. Fr: Endocrinol. Clin., *4*:219, 1963.)

CROUZON SYNDROME

(Craniofacial Dysostosis)

Shallow Orbits, Premature Craniosynostosis, Maxillary Hypoplasia

Originally described in 1912 by Crouzon[1] in a mother and her daughter, this condition usually has an adverse effect on craniofacial development alone.

ABNORMALITIES

Craniofacial. Ocular proptosis due to shallow orbits, with or without divergent strabismus, hypertelorism. Frontal bossing.

Hypoplasia of maxilla with or without curved parrot-like nose, inverted V shape to palate.

Craniosynostosis, especially of coronal, lambdoidal, and sagittal sutures with palpable ridging. Short anterior-posterior and wide lateral dimensions of the cranium may occur.

OCCASIONAL ABNORMALITIES. Peg-shaped widely spaced teeth, partial anodontia, large tongue, deviation of nasal septum, atresia of auditory meatus, deafness. Triangular shape to optic foramina.

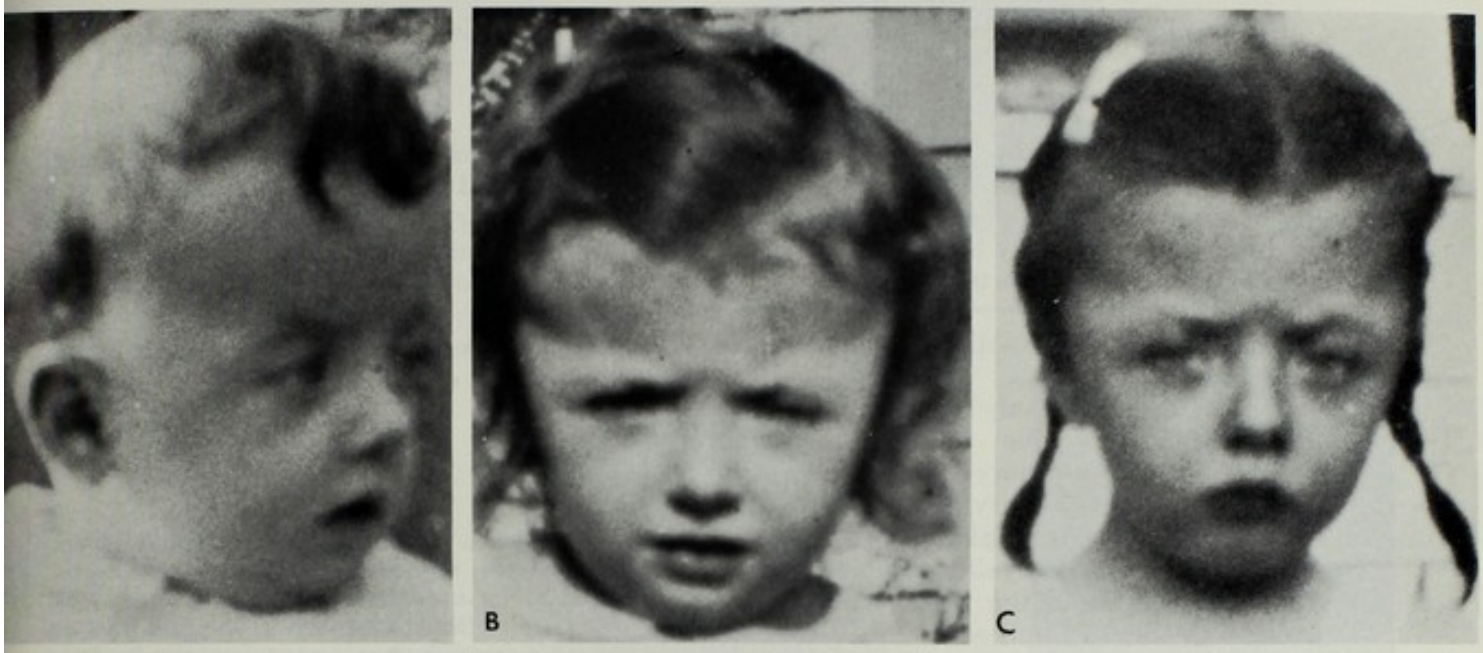
NATURAL HISTORY. The degree of craniosynostosis as well as the age of onset is variable. One infant is described who showed no roentgenographic evidence of craniosynostosis at four months but complete sutural closure by 11 months of age. Surgical morcellation procedures to allow for more normal brain development are indicated when there is increased intracranial pressure. Otherwise, the indications are usually cosmetic and the decision toward surgery is usually mitigated by the severity of the aberrant shape plus the competency of the surgeon who will perform the procedure. Newer techniques allow for cosmetic reconstruction of the facial bones.

Although craniosynostosis limits the growth of the brain, the cranium can undergo some further enlargement even when all sutures are fused at an early age.[5]

ETIOLOGY. Autosomal dominant with variable expression, shallow orbits being the most consistent feature. About one quarter of the reported cases have had a negative family history and presumably represent fresh mutations.

REFERENCES

1. Crouzon, O.: Dysostose cranio-faciale héréditaire. Bull. Mem. Soc. Med. Hop. (Paris), *33*:545, 1912.
2. Dodge, H. W., Jr., Wood, M. W., and Kennedy, R. L. J.: Craniofacial dysostosis: Crouzon's disease. Pediatrics, *23*:98, 1959.
3. Gorlin, R. J., and Pindborg, J. J.: Syndromes of the Head and Neck. New York, McGraw-Hill Book Co., 1964, p. 172.
4. Vulliamy, D. G., and Normandale, P. A.: Craniofacial dysostosis in a Dorset family. Arch. Dis. Child., *41*:375, 1966.
5. Bertelsen, T. I.: The premature synostosis of the cranial sutures. Acta Ophthalmol. [Suppl. 51] (Kbh.), 1958.





The mother of the patient shown in *E* is shown as a young infant *(A)*, at one year of age *(B)*, and at three years of age *(C)*. No surgical procedure was performed, and *D* shows the mother as an adult of normal intelligence with her affected son who had rather severe synostosis of the coronal suture leading to the short cranium. A surgical morcellation procedure was performed on the son's suture. (Courtesy of R. Luce, Group Health Clinic, Seattle.)

SAETHRE-CHOTZEN SYNDROME

(Acrocephalosyndactyly, Type III)

Brachycephaly with Maxillary Hypoplasia, Prominent Ear Crus, Syndactyly

Originally described by Saethre[1] and by Chotzen[2] in the early 1930's, this disorder is only recently being appreciated as a succinct entity.[3] The syndrome has frequently been undiagnosed[4] or misclassified[5] in past reports.

ABNORMALITIES. Variability of almost all features.

Craniofacial. Brachycephaly with high forehead, presumably due to synostosis of coronal suture. Maxillary hypoplasia with narrow palate. Facial asymmetry with deviation of nasal septum. Shallow orbits. Hypertelorism. Ptosis of eyelid. Prominent ear crus extending from the root of the helix across the concha. Small ears.

Limbs. Cutaneous syndactyly, usually partial, most commonly of second-third fingers and/or third-fourth toes. Mild to moderate brachydactyly with clinodactyly of fifth finger. Single upper palmar crease.

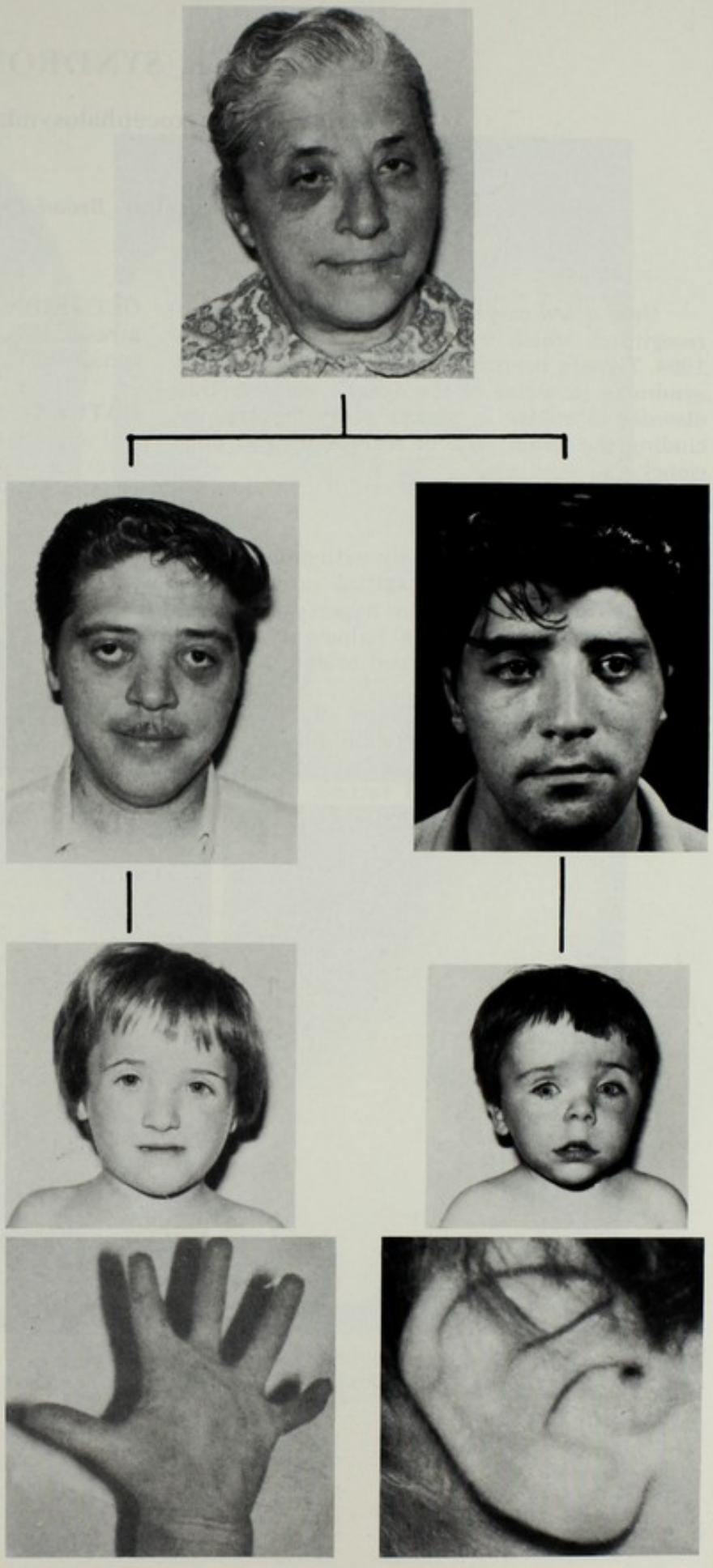
OCCASIONAL ABNORMALITIES. Craniosynostosis to the point of increased intracranial pressure. Mental deficiency, small stature, cleft palate, deafness, strabismus, vertebral anomalies, short fourth metacarpals, presumed cardiac anomaly (murmur), cryptorchidism, renal anomaly.

NATURAL HISTORY. Though most patients are apparently of normal intelligence, mental deficiency of mild to moderate degree has been a feature.[2] Whether this is secondary to craniosynostosis or not remains to be clarified. Facial appearance tends to improve during childhood.

ETIOLOGY. Autosomal dominant with rather wide variance in expression.

REFERENCES

1. Saethre, H.: Ein beitrag zum turmschadelproblem. (Pathogenese, erblichkeit und symptomatologie). Dtsch. Z. Nervenheilkd., *117*:533, 1931.
2. Chotzen, F.: Eine eigenartige familiare Entwicklungsstörung. (Akrocephalosyndaktylie, Dysostosis craniofacialis und Hypertelorismus). Monatsschr. Kinderheilkd., *55*:97, 1932.
3. Bartsocas, C. S., Weber, A. L., and Crawford, J. D.: Acrocephalosyndactyly type III: Chotzen's syndrome. J. Pediatr., *77*:267, 1970.
4. Aase, J. M., and Smith, D. W.: Facial asymmetry and abnormalities of palms and ears: A dominantly inherited developmental syndrome. J. Pediatr., *76*:928, 1970.
5. Gellis, S. S., and Feingold, M.: Atlas of Mental Retardation Syndromes. Washington, D.C., U.S. Department of Health, Education, and Welfare, 1968, p. 26, Figs. 3 and 4.
6. Kreiborg, S., Pruzansky, S., and Pashayan, H.: The Saethre-Chotzen syndrome. Teratology, *6*:287, 1972.



Five affected family members. Note the variable ptosis, facial asymmetry, and strabismus. The hand of the girl shows a simian crease, clinodactyly, and mild webbing between the second and third fingers (the only individual with syndactyly *noted* in this family). The ear of the boy shows the unusually prominent crus across the concha, found in all affected individuals in this family. (From Aase, J. M., and Smith, D. W.: J. Pediatr., 76:928, 1970.)

PFEIFFER SYNDROME

(Pfeiffer type Acrocephalosyndactyly)

Brachycephaly, Mild Syndactyly, Broad Thumbs and Toes

Only a few cases of this disorder have been recognized, which was reported by Pfeiffer in 1964. Though bearing resemblance to the Apert syndrome in terms of the overall pattern, this disorder is milder in almost every feature, including the usual lack of serious mental deficiency.

ABNORMALITIES[1, 2]

Craniofacial. Brachycephaly with craniosynostosis of coronal +/− sagittal sutures with full high forehead, ocular hypertelorism, antimongoloid upslanting palpebral fissures, small nose with low nasal bridge, and narrow maxilla.

Hands. Broad distal phalanges of thumb and big toe, +/− small middle phalanges of fingers, +/− partial syndactyly of second and third fingers and second, third, and fourth toes.

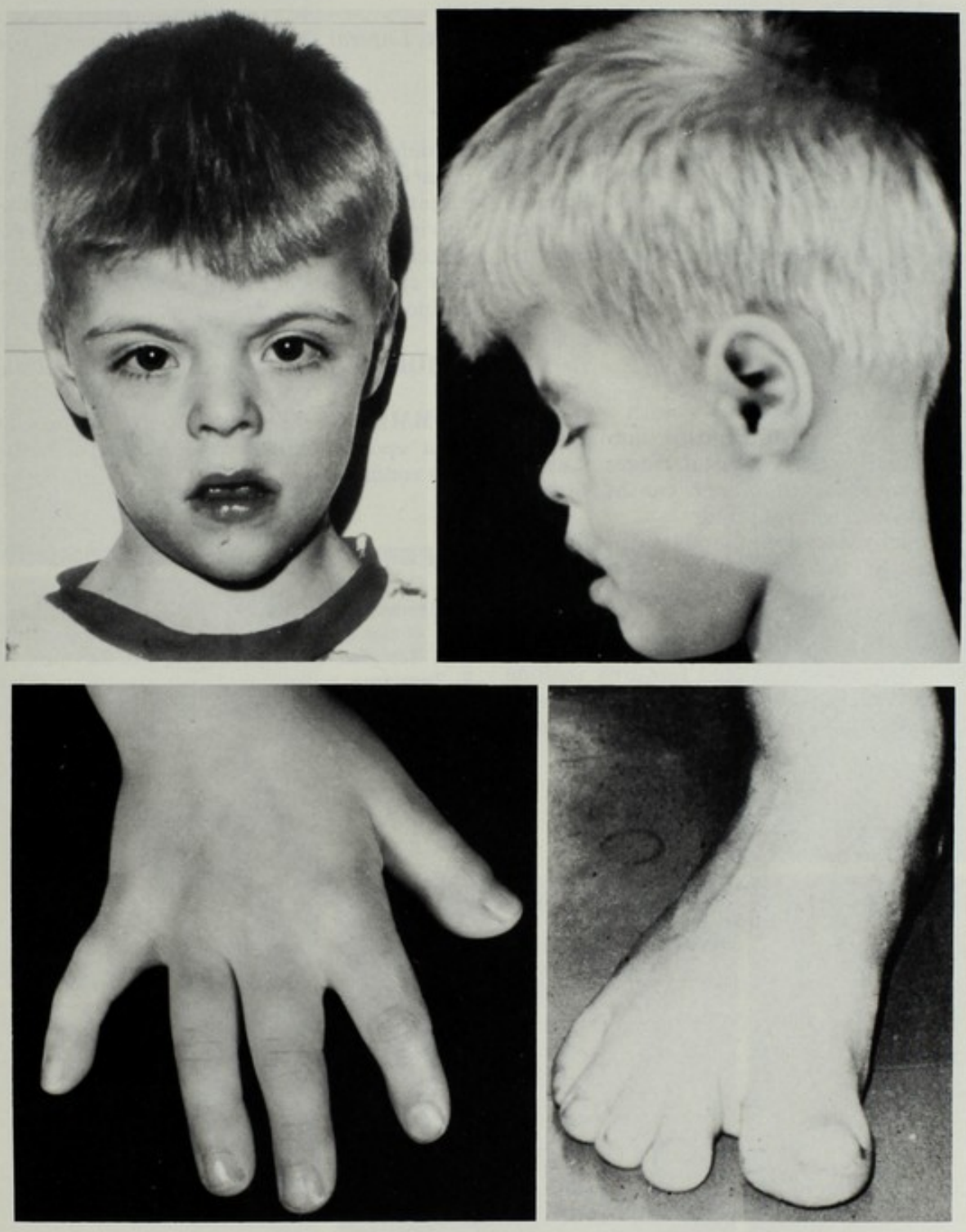
OCCASIONAL ABNORMALITIES. Choanal atresia. Kleeblatschädel anomaly. Radiohumeral synostosis of elbow.

NATURAL HISTORY. With age the craniofacial appearance tends to improve, depending on severity of craniosynostosis. Intelligence has usually been within normal limits.

ETIOLOGY. Autosomal dominant with many cases representing fresh mutations.

REFERENCES

1. Pfeiffer, R. A.: Dominant erbliche Akrocephalosyndactylie. Z. Kinderheilkd., *90*:301, 1964.
2. Martsolf, J. T., Cracco, J. B., Carpenter, G. G., and O Hara, A. E.: Pfeiffer syndrome. An unusual type of acrocephalosyndactyly with broad thumbs and great toes. Am J. Dis. Child., *121*:257, 1971.



Four year old boy with synostosis of coronal sutures and partial sagittal closure, broad thumbs and great toes, and partial syndactyly between second and third fingers and second through fourth toes. (From Martsolf, J. T., et al.: Am. J. Dis. Child., *121*:257, 1971.)

CARPENTER SYNDROME

Acrocephaly, Polydactyly and Syndactyly of Feet, Lateral Displacement of Inner Canthi

Although Carpenter[1] described this condition in 1901, it was not firmly established as an entity until Temtamy's[2] report in 1966. Some of the cases reported in the literature had been mistakenly identified as Apert's syndrome or the Laurence-Moon-Biedl syndrome.

ABNORMALITIES

Growth. Obesity.

Performance. Mental deficiency.

Craniofacial. Brachycephaly with variable synostosis of coronal, sagittal, lambdoid sutures. Shallow supraorbital ridges. Lateral displacement of the inner canthi with or without inner canthal folds.

Limbs. Brachydactyly of hands with clinodactyly and partial syndactyly. Preaxial polydactyly of the feet with partial syndactyly.

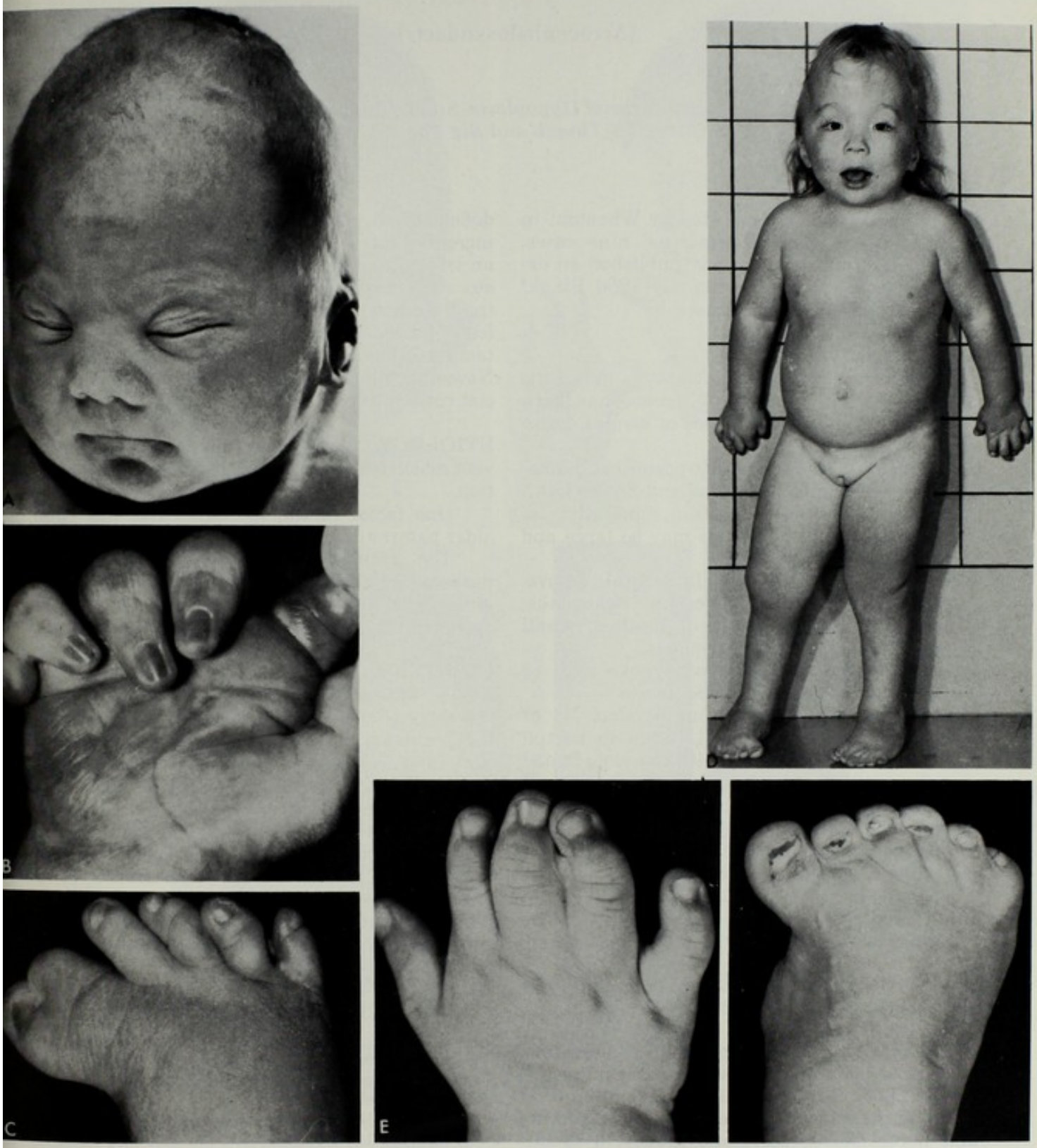
OCCASIONAL ABNORMALITIES. Less consistently observed or reported features include postaxial polydactyly, low-set auricles, congenital heart defect (patent ductus, ventricular septal defect, pulmonic stenosis, transposition), duplication of second phalanx of thumb, metatarsus varus, flat acetabulum, flare to pelvis, coxa valga, genu valgum, lateral displacement of patellae, pilonidal dimple, accessory spleen, abdominal hernias, and generalized aminoaciduria.

ETIOLOGY. Presumed autosomal recessive.

COMMENT. Presently there are inadequate data upon which to base a natural history for this condition.

REFERENCES

1. Carpenter, G.: Two sisters showing malformations of the skull and other congenital abnormalities. Rep. Soc. Study Dis. Child. Lond., *1*:110, 1901.
2. Temtamy, S. A.: Carpenter's syndrome: Acrocephalopolysyndactyly, an autosomal recessive syndrome. J. Pediatr., *69*:111, 1966.



A to *C*, Newborn, necropsy photos. (Courtesy of A. W. Bauer, Group Health Cooperative, Seattle.)
D and *E*, Three year old. (From Temtamy, S. A.: J. Pediatr., *69*:111, 1966.)

APERT SYNDROME

(Acrocephalosyndactyly)

Irregular Craniosynostosis, Midfacial Hypoplasia, Syndactyly, and Broad Distal Phalanx of Thumb and Big Toe

The condition was reported by Wheaton[1] in 1894, in 1906 Apert[2] summarized nine cases, and in 1920 Park and Powers[3] published an exceptional essay on this entity. By 1960 Blank[4] noted the recording of 150 cases.

ABNORMALITIES

Performance. Mental deficiency may be present, but normal intelligence has been observed and the incidence of mental defect is not known.

Craniofacial. Short anterior-posterior diameter with high full forehead and flat occiput.

Irregular craniosynostosis, especially of coronal suture. Fontanels may be large and late in closure.

Flat facies, supraorbital horizontal groove, shallow orbits, hypertelorism, strabismus, downslanting of palpebral fissures, small nose, and maxillary hypoplasia.

Narrow palate with median groove with or without cleft palate or bifid uvula.

Limbs. Osseous or cutaneous syndactyly, or both, varying from total fusion to partial fusion; most commonly with complete fusion of second, third, and fourth fingers. Distal phalanges of the thumbs are often broad and in valgus position. Fingers may be short. Cutaneous syndactyly of all toes with or without osseous syndactyly. Distal hallux may be broad and malformed.

Skin. Moderate to severe acne, including the forearms, at adolescence.

OCCASIONAL ABNORMALITIES. Short humerus, synostosis of radius and humerus, and limitation of joint motility.

Pyloric stenosis, ectopic anus, pulmonary aplasia, atrophy of pulmonary arteries, anomalous tracheal cartilage, pulmonic stenosis overriding aorta, ventricular septal defect, endocardial fibroelastosis, polycystic kidney, hydronephrosis, and bicornuate uterus.

NATURAL HISTORY. There are no adequate data on the long-term follow-up of patients. Early surgery for craniosynostosis, however, would seem indicated when the condition is of sufficient magnitude to give rise to increased intracranial pressure. Though there can be mental deficiency in patients who have no evidence of increased intracranial pressure, mental defect is an irregular occurrence. There should be vigorous early management of the syndrome. When the thumb is immobilized, early surgery to allow for a pincer grasp is indicated, with later attempts at further improvement of hand function. Newer techniques allow for vastly improved facial cosmetic reconstruction.

ETIOLOGY. Autosomal dominant with the vast majority of cases representing a fresh mutation.

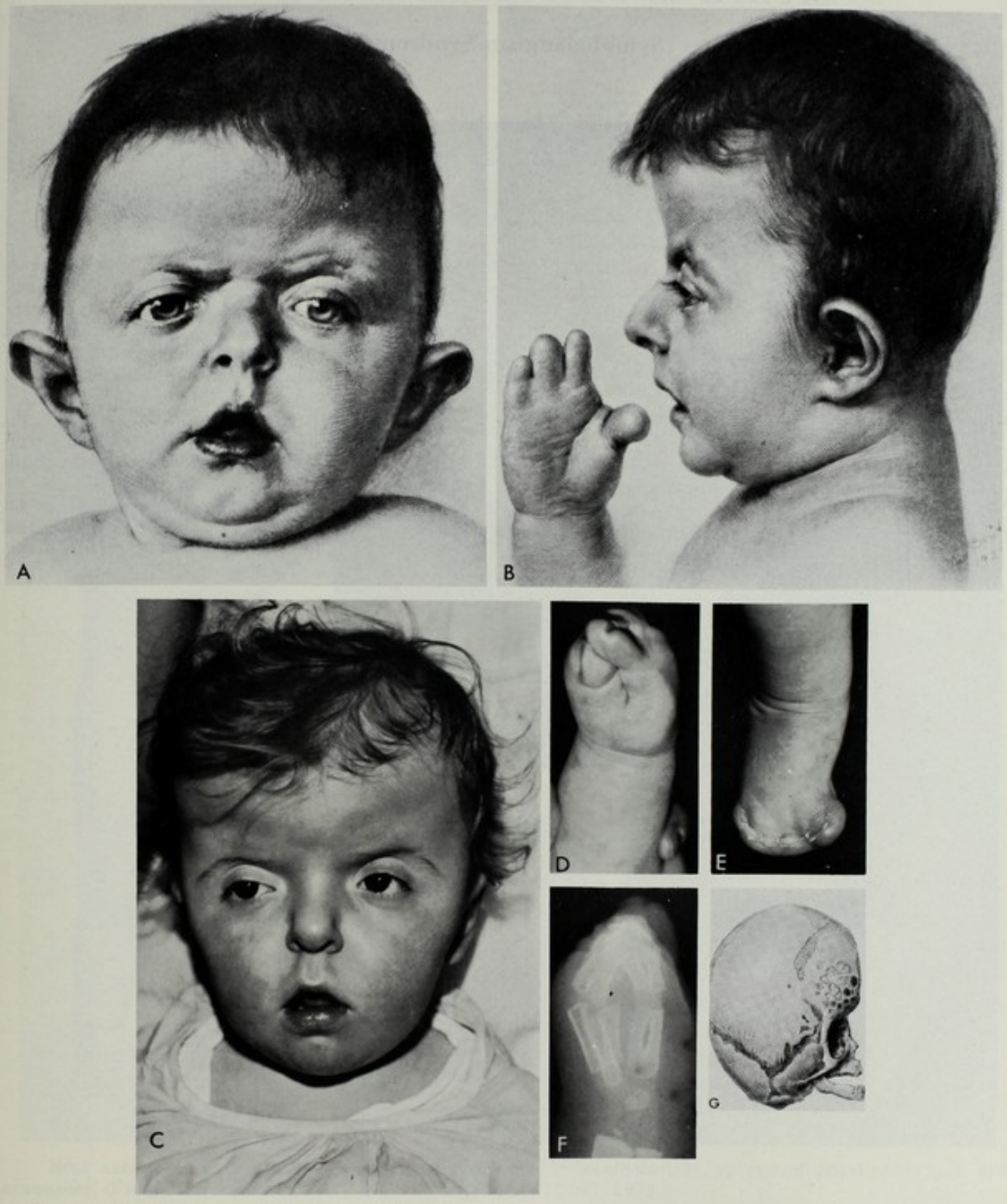
One factor in the sporadic cases has been older paternal age.

The recurrence risk for the unaffected parents of a child with Apert syndrome is negligible, whereas the recurrence risk for the offspring of the affected individual is 50 per cent.

COMMENT. The osseous developmental pathology appears to be irregular bridging between the early islands of mesenchymal blastema that will become bone, especially in the distal extremities and cranium. Indications of hypoplasia and abnormal shape of bone are also evident and the mutant gene may adversely affect the organization of other tissues. This is evident in the irregular occurrence of mental deficiency and the greater than expected concurrence of a number of nonskeletal malformations. Therefore, every newborn suspected of having Apert syndrome deserves a complete evaluation for other malformations.

REFERENCES

1. Wheaton, S. W.: Two specimens of congenital cranial deformity in infants associated with fusion of the fingers and toes. Trans. Path. Soc. London, *45*:238, 1894.
2. Apert, E.: De l'Acrocéphalosyndactylie. Bull. Soc. Med., *23*:1310, 1906.
3. Park, E. A., and Powers, G. F.: Acrocephaly and scaphocephaly with symmetrically distributed malformations of the extremities. A study of the so-called "Acrocephalosyndactylism." Am. J. Dis. Child., *20*:235, 1920.
4. Blank, C. E.: Apert's syndrome (a type of acrocephalosyndactyly) observations on British series of thirty-nine cases. Ann. Hum. Genet., *24*:151, 1960.



A and *B*, A boy, drawn by the late M. Brödel.

C, Two year old girl, her hand *(D)*, foot *(E)*, and x-ray of the hand *(F)*.

G, The cranium of an infant with Apert syndrome, showing the irregular synostosis of the coronal suture and the aberrant development in the frontal bone.

(*A*, *B*, and *G* from Park, E. A., and Powers, G. F.: Am. J. Dis. Child., *20*:235, 1920.)

MULTIPLE SYNOSTOSIS SYNDROME

(Symphalangism Syndrome)

Symphalangism, Hypoplasia of Alae Nasae

In the past this disorder was generally termed symphalangism (synostosis of finger joints), a nonspecific anomaly.[1-3] The multiple synostosis character of the disorder herein set forth was emphasized by Maroteaux, et al.[4]

ABNORMALITIES

Facies. Narrow, with hypoplasia of alae nasae.

Limbs. Multiple fusion of midphalangeal joints, elbow, and carpal and tarsal bones (especially navicular to talus). Variable brachydactyly and distal bone hypoplasia or aplasia in phalanges.

Middle Ear. Variable fusion of middle ear ossicles with conductive deafness.

ETIOLOGY. Autosomal dominant with appreciable variance in expression.

REFERENCES

1. Vesell, E. S.: Symphalangism, strabismus and hearing loss in mother and daughter. N. Eng. J. Med., *263*:839, 1960.
2. Fuhrmann, W., Steffens, C., Schwarz, G., and Wagner, A.: Dominant erbliche Brachydaktylie mit Gelenksaplasien. Humangenetik, *1*:337, 1965.
3. Strasburger, A. K., Hawkins, M. R., Eldridge, R., Hargrave, R. L., and McKusick, V. A.: Symphalangism: Genetic and clinical aspects. Bull. Johns Hopkins Hosp., *117*:108, 1965.
4. Maroteaux, P., Bouvet, J. P., and Briard, M. L.: La maladie des synostoses multiples. Nouv. Presse Med., *1*:3041, 1972.



Note narrow nose, prominent external ear and variable brachydactyly, aplasia of distal phalanges, and synostoses. (From Maroteaux, P., et al.: Nouv. Presse Med., *1*:3041, 1972.)

MULTIPLE EXOSTOSES SYNDROME

(Diaphyseal Aclasis, External Chondromatosis Syndrome)

Diaphyseal Outgrowths Leading to Limb Deformity, with or without Short Metacarpals

More than 1000 cases have been reported.[1]

ABNORMALITIES[1, 2]

Skeletal. Diaphyseal juxtaepiphyseal outgrowths develop, capped by hyaline cartilage, and tend to grow away from the joint, leading to deformity. Though often present at birth, they are usually not appreciated until early childhood. There is a slowing in their growth at adolescence and no further growth occurs in the adult. They are most prominent at ends of long bones, especially at the knee, with variable involvement of pelvis, scapulae, and ribs. Involved bone may be relatively short, especially the ulna, with consequent bowing of the forearm. Shortness of stature is a variable feature, with the mean male adult height being 169 cm and that of the female being 159 cm.

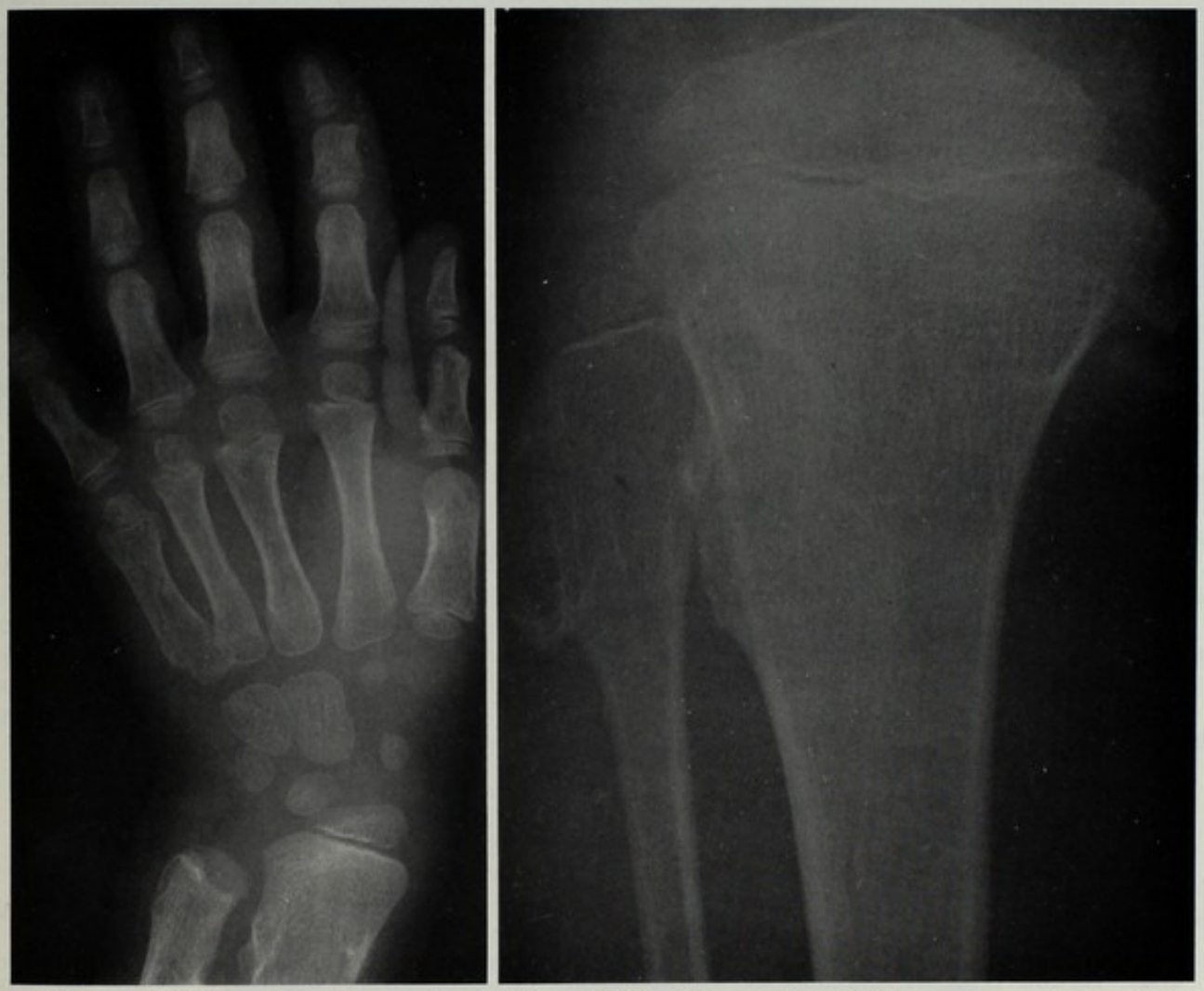
OCCASIONAL ABNORMALITY. Enchondromata. Short metacarpal (4–5) bones.

NATURAL HISTORY. New outgrowths and enlargement of old exostoses may occur through the age of adolescence. Thereafter no further growth takes place, although there is a 2 to 10 per cent incidence of sarcoma from such lesions in the adult, a risk that does not pertain to childhood.

ETIOLOGY. Autosomal dominant, with 62 per cent of cases being familial.

REFERENCES

1. Solomon, L.: Hereditary multiple exostosis. Am. J. Hum. Genet., *16*:351, 1964.
2. Rubin, P.: Dynamic Classification of Bone Dysplasias. Chicago, Year Book Medical Publishers, 1964, p. 297.



Six year old. Outgrowths from proximal tibia and fibula, less prominently from radius and ulna. Note the short midphalanx of the fifth finger and the irregular midphalanx of the index finger.

NAIL-PATELLA SYNDROME

(Hereditary Osteo-Onychodysplasia)

Nail Dysplasia, Patella Hypoplasia, Iliac Spurs

Little's[1] report in 1897, limited to a presentation of patellar defect, is usually credited as the initial description of this syndrome, whereas this pattern includes multiple other dysplasias of osseous as well as nonosseous mesenchymal tissues. More than 200 cases have been reported.

ABNORMALITIES. Relative frequency of expression as percentages.

Nail. Hypoplasia, splitting, most commonly of thumbnail	98%
Knee. Hypoplastic to absent patella, hypoplasia of lateral femoral condyle and small head of fibula	92%
Elbow. Hypoplastic capitellum, small head of radius	90%
Ilium. Spur in mid-posterior ilium, 71 per cent palpable	81%
Scapula. Hypoplasia, convex thick outer border	44%
Iris. Dark, "clover-leaf" pigmentation at inner margin	46%
Renal. Proteinuria with or without hematuria, casts, renal insufficiency	30%

Other Frequent Features. Absence of dorsal distal phalangeal joints, delayed ossification of secondary centers of ossification, valgus of femoral neck, club foot.

OCCASIONAL ABNORMALITIES

Skeletal. Prominent outer clavicle, malformed sternum, spina bifida, scoliosis, enlarged ulnar styloid process, clinodactyly of fifth finger, dislocation of head of radius.

Eye. Keratoconus, microcornea, microphakia, cataract, ptosis.

Muscle. Aplasia of pectoralis minor, biceps, triceps, quadriceps.

Central Nervous System. Occasional mental deficiency, psychosis.

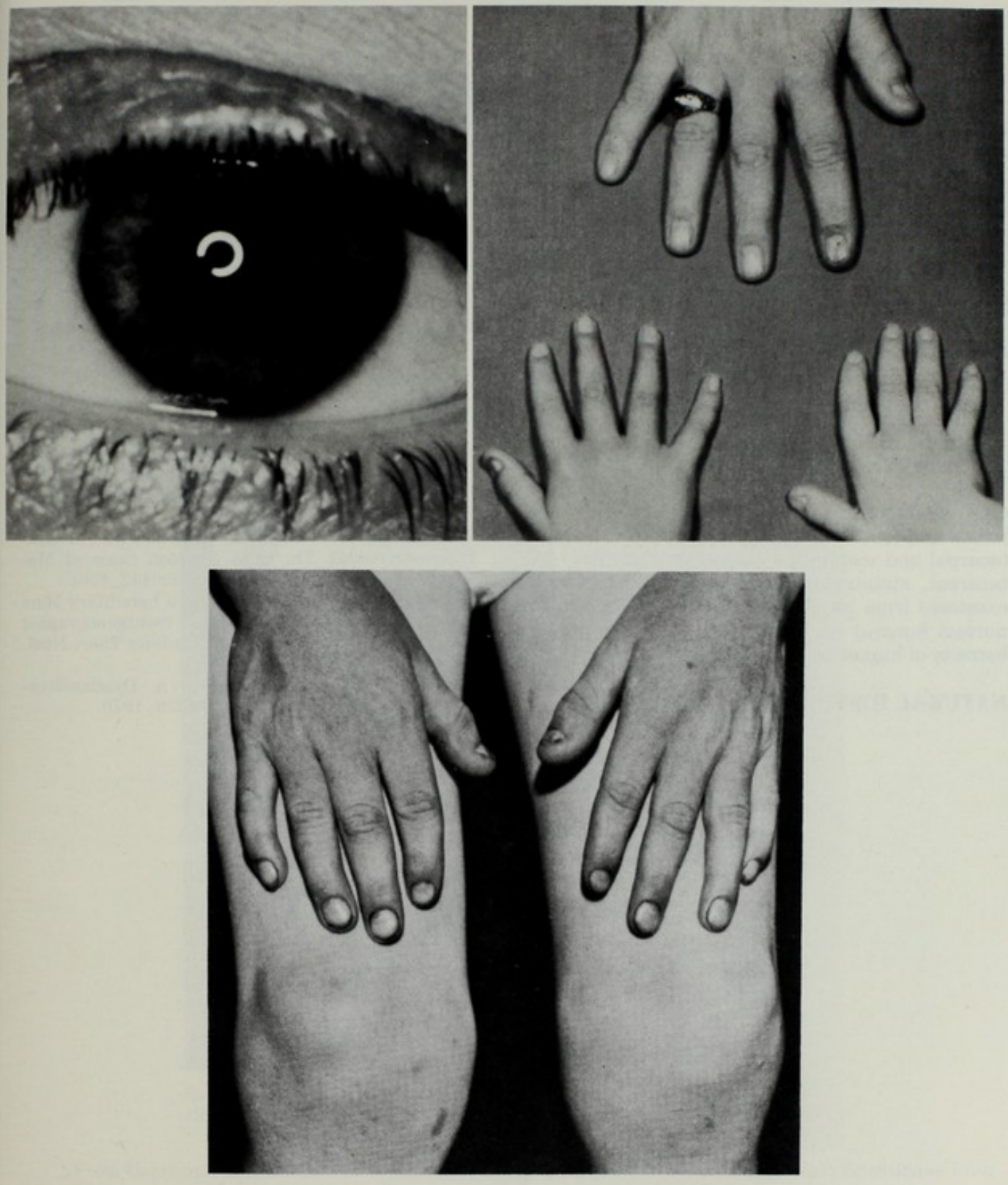
NATURAL HISTORY. Patients may have problems owing to limitation of joint motility, dislocation, or both, especially at the elbow and knee where osteoarthritis may eventually limit function. Children should be closely followed for scoliosis. Albuminuria is the most common early indication of a renal problem. Studies show hyaline thickening of the glomerular basement membrane, cause unknown. Renal failure is apparently rare prior to the fourth decade.

ETIOLOGY. Autosomal dominant, always showing some expression. Close linkage with the genetic determinants of ABO blood group substances. A closer correlation for the extent of nail dysplasia has been found among affected siblings than between affected parent and offspring. This evidence implies a strong effect of the normal allele (always derived from the unaffected parent) on the expression of the mutant allele for the nail-patella syndrome.

COMMENT. The osseous abnormality consists of specific regions of hypoplasia such as the lateral knee and elbow, and other specific regions of hyperplasia such as the iliac spurs. The latter defect, as yet unknown in any animal or in other diseases of man, appears to be pathognomonic as an expression of this mutant gene.

REFERENCES

1. Little, E. M.: Congénital absence or delayed development of the patella. Lancet, *2*:781, 1897.
2. Carbonara, P., and Alpert, M.: Hereditary osteo-onycho-dysplasia (Hood). Am. J. Med. Sci., *248*: 139, 1964.
3. Lucas, G. L., and Opitz, J. M.: The nail-patella syndrome. Clinical and genetic aspects of 5 kindreds with 38 affected family members. J. Pediatr., *68*:273, 1966.
4. Darlington, D., and Hawkins, C. F.: Nail-patella syndrome with iliac horns and hereditary nephropathy. Necropsy report and anatomical dissection. J. Bone Joint Surg. (Br.), *49-B*:164, 1967.
5. Beals, R. K., and Eckardt, A. L.: Hereditary onycho-osteodysplasia. A report of nine kindreds. J. Bone Joint Surg. [Am.], *51*:505, 1969.



Upper left, Aberrant patterning of inner iris.
Upper right, Father and two affected offspring showing nail hypoplasia, most striking for the thumbnails.
Below, Adolescent showing nail hypoplasia, especially of thumbs, and displacement of small patellae. (Courtesy of J. Opitz, University of Wisconsin.)

LERI-WEILL DYSCHONDROSTEOSIS SYNDROME

Short Forearms with Madelung Deformity, with or without Short Lower Leg

Leri and Weill[1] described this condition in 1929, and more than 30 cases have been reported subsequently. Most patients previously categorized as having Madelung's deformity are examples of this entity.

ABNORMALITIES

Growth. Variable small stature, adult height from 135 cm to normal.

Extremities. Short forearm with bowing of radius, widened gap between radius and ulna and altered osseous alignment at wrist. May have partial dislocation of ulna at wrist, elbow, or both, with limitation of movement. Short lower leg.

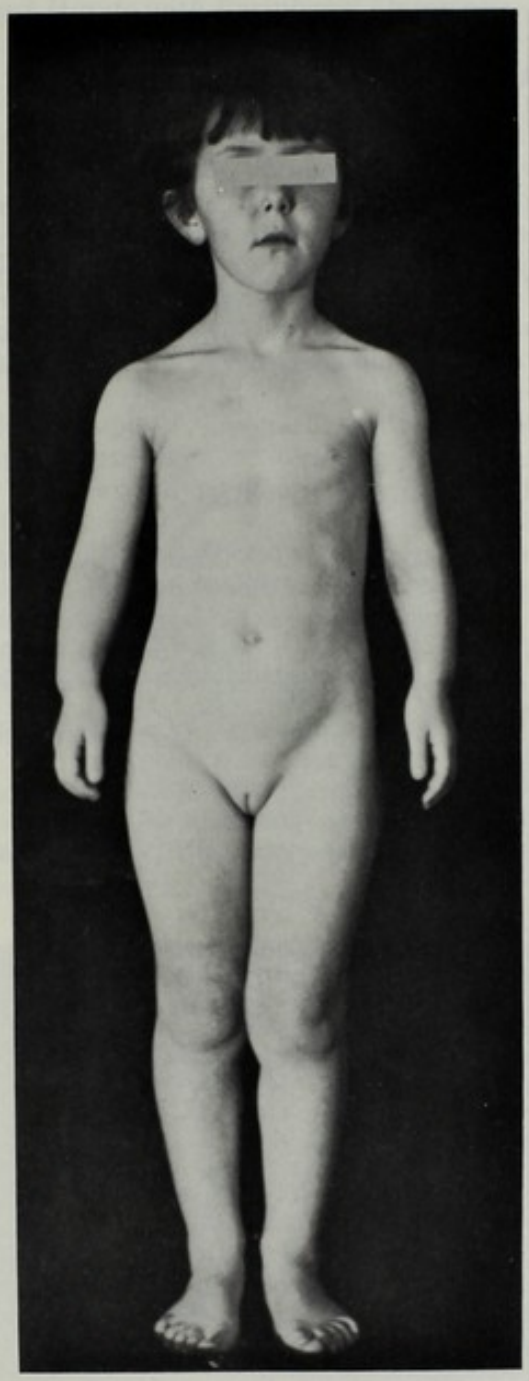
OCCASIONAL ABNORMALITIES. Short hands and feet with metaphyseal flaring in metacarpal and metatarsal bones, short fourth metacarpal, metatarsal bones, curvature of tibia, exostoses from proximal tibia and/or fibula, abnormal femoral neck, coxa valga, abnormal tuberosity of humerus.

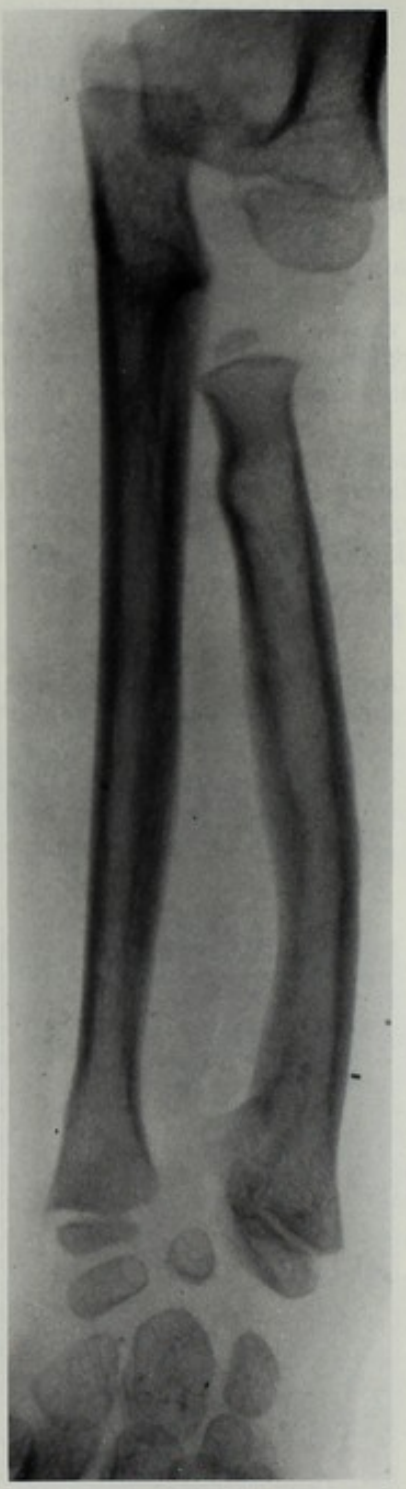
NATURAL HISTORY. Becker has noted associated paramyotonia in affected individuals in one family; it remains to be determined whether or not this is a frequent feature. Otherwise the only usual problems are moderate shortness of stature and limitation of joint mobility at the wrist, elbow, or both.

ETIOLOGY. Autosomal dominant with an excess of affected females in the recorded cases.

REFERENCES

1. Leri, A., and Weill, J.: Une affection congenitale et symetrique du developpement osseus: la dyschondrosteose. Bull. Mem. Soc. Med. Hop. (Paris), *45*:1491, 1929.
2. Herdman, R. C., Langer, L. O., Good, R. A.: Dyschondrosteosis. The most common cause of Madelung's deformity. J. Pediatr., *68*:432, 1966.
3. Langer, L. O.: Dyschondrosteosis, a hereditary bone dysplasia with characteristic roentgenographic features. Am. J. Roentgenol. Radium Ther. Nucl. Med., *45*:178, 1965.
4. Felman, A. H., and Kirkpatrick, J. A.: Dyschondrosteoses. Am. J. Dis. Child., *120*:329, 1970.





Seven and five twelfths years.
Height age: Five and one half years.

(From Lamy and Maroteaux: Les chondrodystrophies génotypiques. Paris, L'Expansion Scientifique Française, 1960.)

LANGER MESOMELIC DWARFISM SYNDROME

(Homozygous Leri-Weill Dyschondrosteosis Syndrome)

Mesomelic Dwarfism, Rudimentary Fibula, Micrognathia

Langer[1] summarized this disorder as a distinctive entity in 1967, citing numerous cases from past literature, the original report being by Brailsford.[3]

ABNORMALITIES

Facies. Small mandible.

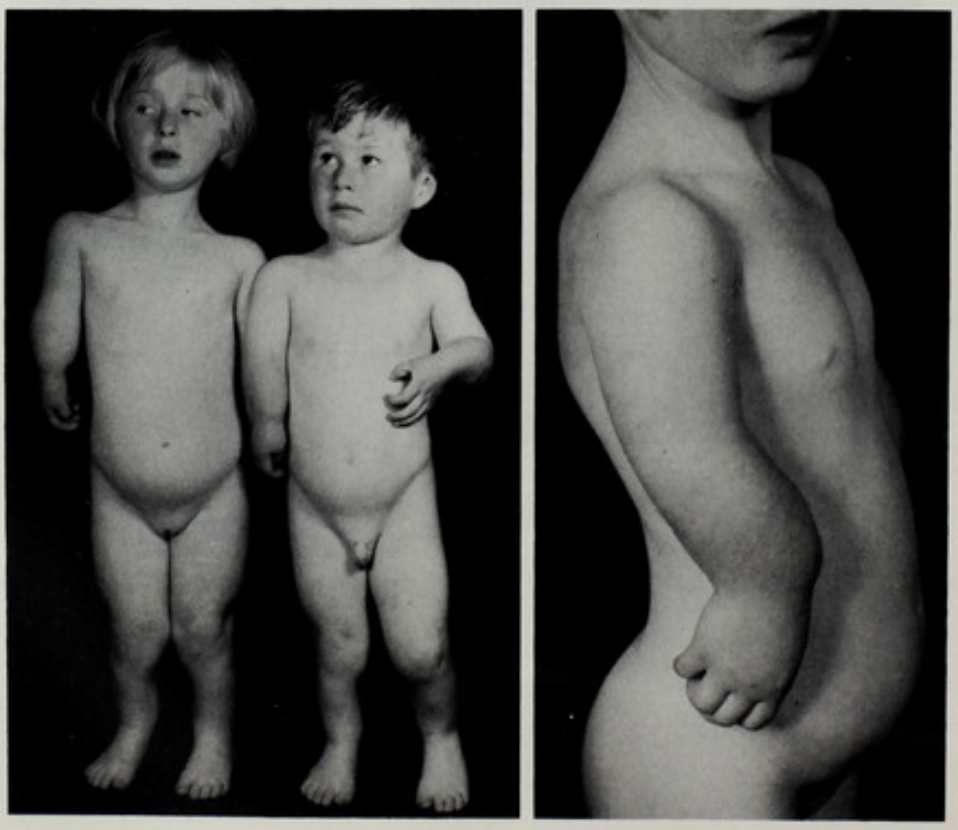
Limbs. Short, especially forearms and lower legs (mesomelia) with undue hypoplasia of fibula and sometimes ulna.

NATURAL HISTORY. One adult male was 130 cm tall. Normal intelligence with surprisingly good function.

ETIOLOGY. Autosomal recessive. Espiritu, et al.[4] set forth rather convincing evidence that this disorder can occur as the homozygous state of the autosomal dominant Leri-Weill Dyschondrosteosis syndrome. Heterozygote individuals with the latter disorder have mild to moderate shortness of stature and relatively short forearms with the Madelung deformity. The homozygous state is a much more severe shortness of stature with striking smallness of the forearms and lower legs (mesomelia) plus the additional feature of micrognathia.

REFERENCES

1. Langer, L. O.: Mesomelic dwarfism of the hypoplastic ulna, fibula, mandible type. Radiology, *89*:654, 1967.
2. Blockey, N. J., and Lawrie, J. H.: An unusual symmetrical distal limb deformity in siblings. J. Bone Joint Surg. [Br.], *45*:745, 1963.
3. Brailsford, J. F.: Dystrophies of the skeleton. Br. J. Radiol., *8*:533, 1935.
4. Espiritu, C., Chen, H., and Woolley, P. V., Jr.: Probable homozygosity for the dyschondrosteosis genes. Am. J. Dis. Child., *129*:375, 1975.



Siblings with unusual shortness of stature with disproportionate smallness of forearms and lower legs, especially the ulnae and fibulae. (From Blockley, N. J., and Lawrie, J. H.: J. Bone Joint Surg.[Br.], *45*:745, 1963.)

ACRODYSOSTOSIS SYNDROME

Short Hands with Peripheral Dysostosis, Small Nose, Mental Deficiency

Maroteaux and Malamut[1] first described this disorder in three patients in 1968 and there are now over 20 published cases.

ABNORMALITIES[1, 2]

Growth. Mild to moderate prenatal onset growth deficiency.

Performance. Mental deficiency in about 90 per cent.

Craniofacial. Brachycephaly, low nasal bridge, broad and small upturned nose, tendency to hold mouth open, and hypoplastic maxilla with prognathism.

Limbs. Short, especially distally with progressive deformity in distal humerus, radius, and ulna, and cone-shaped epiphyses which fuse prematurely in hands and feet. Hands appear short and broad with wrinkling of dorsal skin.

OCCASIONAL ABNORMALITIES. Epicanthal folds, hypertelorism, optic atrophy, dimpled nasal tip, malocclusion of teeth, calvarial hyperostosis, hydrocephalus, recurrent ear infections with occasional hearing loss, pigmented nevi, hypogenitalism, hypogonadism, dislocated radial heads, small vertebrae which may collapse, spinal curvatures.

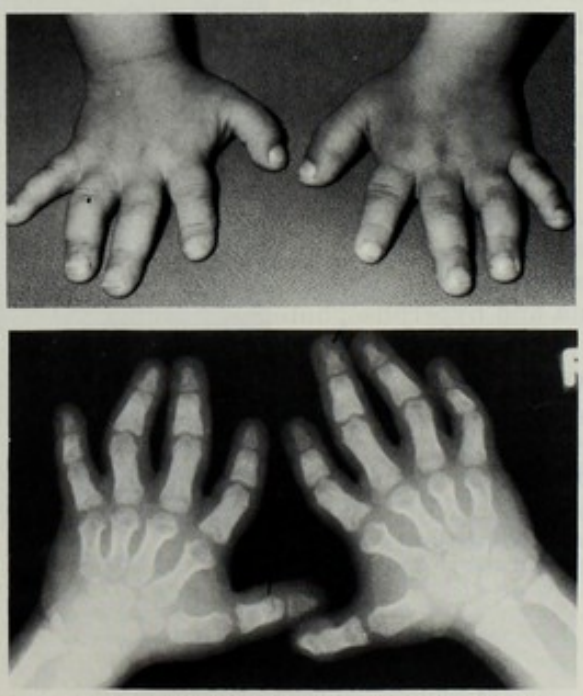
NATURAL HISTORY. Most patients do relatively well save for the problems of mental deficiency and arthritic complaints. Progressive restriction of movement of the hands, elbows, and spine may occur.

ETIOLOGY. Unknown, sporadic occurrence. Older paternal age suggests autosomal dominant fresh mutation.

REFERENCES

1. Maroteaux, P., and Malamut, G. L.: L'acrodysostose. Press Med., *76*:2189, 1968.
2. Robinow, M., Pfeiffer, R. A., Gorlin, R. J., McKusick, V. A., Renuart, A. W., Johnson, G. F., and Summitt, R. L.: Acrodysostosis. A syndrome of peripheral dysostosis, nasal hypoplasia, and mental retardation. Am. J. Dis. Child., *121*:195, 1971.





Five year old female. Note the low nasal bridge, epicanthal folds, and the prominent mandible, short broad fingers with skin wrinkling, and the broad and short metacarpals and phalanges with cone-shaped epiphyses.

ALBRIGHT HEREDITARY OSTEODYSTROPHY SYNDROME

(Pseudohypoparathyroidism, Pseudopseudohypoparathyroidism)

Short Metacarpal, Rounded Facies, with or without Hypocalcemia and/or Vicarious Mineralization

Albright[1] described this condition in 1942 and referred to it as pseudohypoparathyroidism because of hypocalcemia and hyperphosphatemia that were unresponsive to parathormone. Subsequently patients were detected with a comparable phenotype but with normocalcemia, even in the same family as a patient with hypocalcemia. The term pseudopseudohypoparathyroidism was utilized to designate such instances. Because it is now obvious that hypocalcemia is a variable expression in this hereditable disease, the term Albright's hereditary osteodystrophy seems preferable. More than 100 cases have been reported.

ABNORMALITIES

Growth. Small stature; final height, 54 inches to 5 feet; occasionally taller. Obesity, moderate.

Performance. Mental deficiency, intelligence quotient of 20 to 99, mean I.Q. about 60; occasionally normal.

Facies. Rounded, low nasal bridge.

Dentition. Delayed dental eruption, aplasia, and/or enamel hypoplasia.

Limbs. Short metacarpals and metatarsals, especially the fourth and fifth. Cone-shaped epiphyses.

Extra Skeletal Calcification. Areas of mineralization in subcutaneous tissues, basal ganglia.

Calcium and Phosphorus. Variable hypocalcemia and hyperphosphatemia.

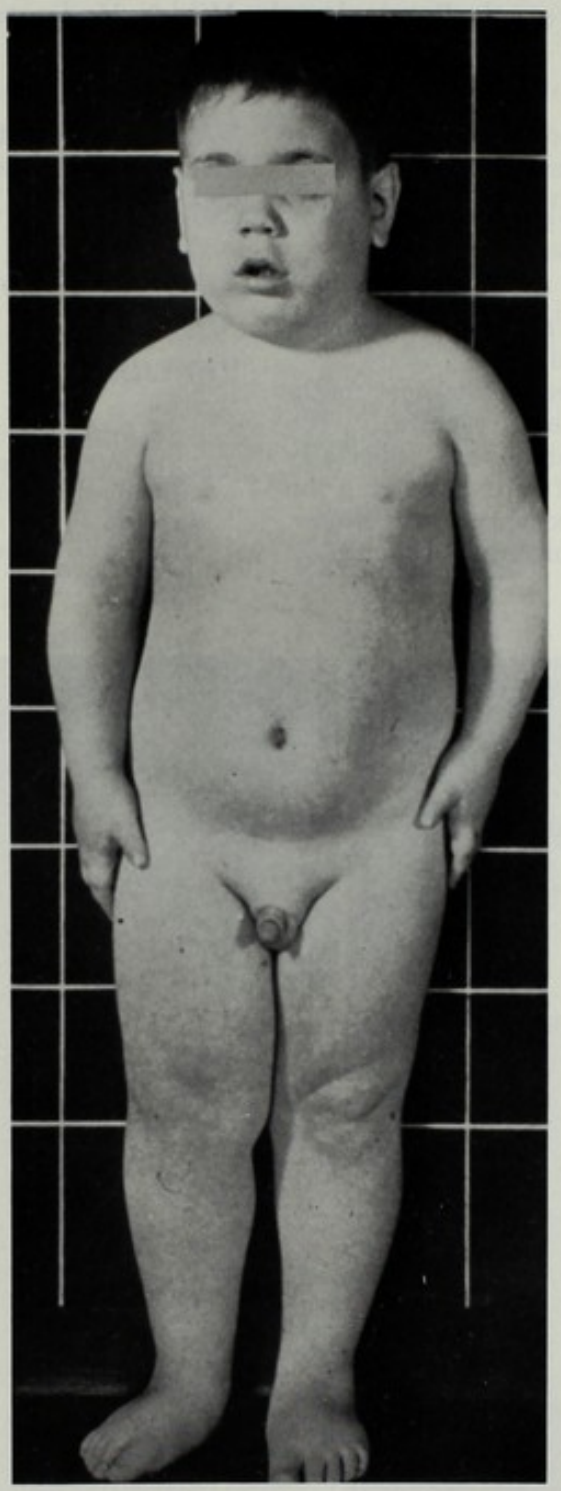
OCCASIONAL ABNORMALITIES. Distal palmar axial triradii, osteochondromata, thick calvarium, short ulna, short phalanges, epiphyseal dysplasia, genu valgum, hypothyroidism, hypogonadism with or without gonadal dysgenesis, peripheral lenticular opacities.

NATURAL HISTORY. Hypocalcemia, when present, usually becomes evident in childhood, seizures being the most common presenting symptom. Cautious vitamin D therapy in dosage of 25,000 to 100,000 units per day may be necessary; however, the therapy should be discontinued every few years to reassess the situation, because spontaneous amelioration of the hypocalcemia may occur with time.

ETIOLOGY. The family data are indicative of a single mutant gene giving rise to this syndrome. The findings of a 2:1 female to male sex incidence have favored an X-linked dominant mode of determination.

REFERENCES

1. Albright, F., Burnett, C. H., Smith, P. H., and Parson, W.: Pseudohypoparathyroidism—an example of 'Seabright-bantam syndrome.' Report of three cases. Endocrinology, *30*:922, 1942.
2. Mann, J. B., Alterman, S., and Hills, A. G.: Albright's hereditary osteodystrophy comprising pseudohypoparathyroidism and pseudopseudohypoparathyroidism. With a report of two cases representing the complete syndrome occurring in successive generations. Ann. Intern. Med., *56*:315, 1962.
3. Miller, J. Q., Rostafiniski, M. J., and Hyde, M. S.: Gonadal dysgenesis and brachymetacarpal dwarfism (pseudopseudohypoparathyroidism). Arch. Intern. Med., *116*:940, 1965.
4. Christiaen, L., Gontaine, G., Farriaux, J. P., and Biserte, G.: Le pseudohypoparathyroidisme chronique. À propos de trois cas familiaux. Acta Paediatr. Belg., *21*:5, 1967.
5. Steinbach, H. L., and Young, D. A.: The roentgen appearance of pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism. Am. J. Roentgenol. Radium Ther. Nucl. Med., *97*:49, 1968.



Five year old with height age of three and one half years and bone age of five years. Hypocalcemia and hyperphosphatemia were first detected at one year of age.

BRACHYDACTYLY SYNDROME, TYPE E

Short Metacarpals, Brachydactyly, Mild to Moderate Short Stature

In 1951 Bell[1] classified genetic forms of brachydactyly into five types, A to E. Riccardi and Holmes[2] have recently summarized the findings in type E.

ABNORMALITIES

Growth. Mild to moderate shortness of stature with relatively short limbs.

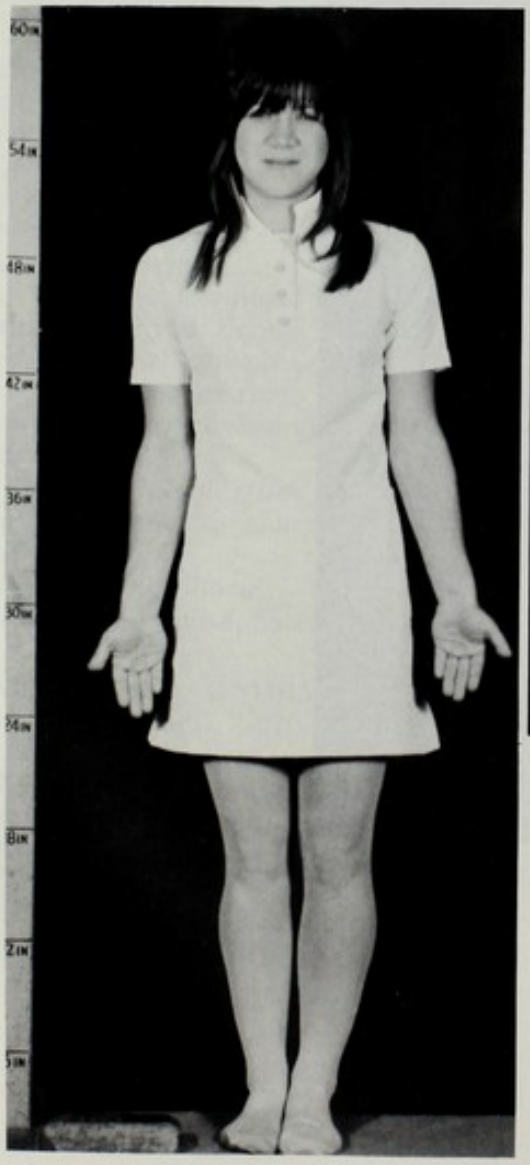
Limbs. Short hands and feet with short metacarpals and metatarsals, especially the fourth and fifth; short phalanges, especially the terminal phalanx of thumb and big toe and the middle phalanx of the fifth finger. Variable cone-shaped epiphyses in hand.

NATURAL HISTORY. Small size is usually evident by birth with a consistently slow pace of postnatal growth.

ETIOLOGY. Autosomal dominant.

REFERENCES

1. Bell, J.: On brachydactyly and symphalangism. *In* Treasury of Human Inheritance, Vol. V, London, Cambridge University Press, 1951, pp. 1–31.
2. Riccardi, V. M., and Holmes, L. B.: Brachydactyly, type E. J. Pediatr., *84*:251, 1974.





Mildly short young woman who has small hands with disproportionate shortness of metacarpals, some phalanges and indented epiphyses (cone-shaped) in some phalanges. (From Riccardi, V. M., and Holmes, L. B.: J. Pediatr., *84*:251, 1974.)

WEILL-MARCHESANI SYNDROME

(Brachydactyly-Spherophakia Syndrome)

Brachydactyly, Small Spherical Lens, Short Stature

More than 18 instances of this condition have been described since the initial recognition by Weill in 1932 and the broader description by Marchesani in 1939.

ABNORMALITIES

Growth. Small stature.

Craniofacial. Broad skull, small shallow orbits, mild maxillary hypoplasia with narrow palate.

Eye. Small spherical lens, myopia with or without glaucoma, ectopia lentis in half of cases, blindness in one third.

Teeth. Malformed and malaligned.

Limbs. Brachydactyly with broad metacarpals and phalanges, with or without late ossification of epiphyses.

OCCASIONAL ABNORMALITY. Cardiac anomaly.

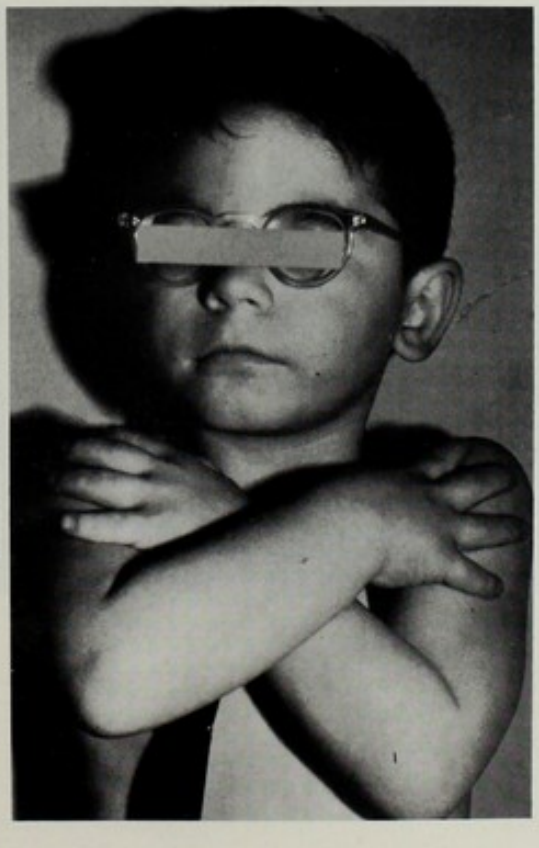
NATURAL HISTORY. The mean age of recognition of an ocular problem in this disorder is 7.5 years, the youngest recorded age being nine months. Dilatation of the pupil is often necessary to appreciate the lens defect. Intelligence is usually not affected.

ETIOLOGY. Autosomal recessive inheritance implied.

REFERENCES

1. Weill, G.: Ectopie du cristallin et malformations generales. Ann. Ocul. (Paris), *169*:21, 1932.
2. Marchesani, O.: Brachydaktylie und angeborene Kugellinse als Systemerkrankung. Klin. Monatsbl. Augenheilkd., *103*:392, 1939.
3. Zabriskie, J., and Reisman, M.: Marchesani syndrome. J. Pediatr., *52*:158, 1958.
4. Feinberg, S. B.: Congenital mesodermal dysmorphodystrophy (brachymorphic type). Radiology, *74*:218, 1960.





Nine year old with height age of five and one half years. Small lens and myopia. (From Zabriskie, J., and Reisman, M.: J. Pediatr., *52*:158, 1958.)

BEALS AURICULO-OSTEODYSPLASIA SYNDROME

Hypoplasia of Capitellum, Attached Ear Lobule, Short Stature

Beals described this disorder in 29 affected individuals in two families in 1967.[1]

ABNORMALITIES

Growth. Mild to moderate short stature.

Ears. Elongated attached lobules with small posteriorly placed lobule at point of attachment.

Elbow. Hypoplasia of capitellum with or without dislocation of radius.

Shoulder. Broad shoulders with wide base of neck and horizontal alignment of clavicles.

OCCASIONAL ABNORMALITIES. Dislocation of hip in one third of affected females. Short carpal area of wrist with ulnar slope to distal radius.

NATURAL HISTORY. Patients tend to be below the 50th percentile for stature. Other than variable dislocation of the hip and arthritic manifestations of the elbow, affected individuals are in good health.

ETIOLOGY. Autosomal dominant inheritance.

REFERENCES

1. Beals, R. K.: Auriculo-osteodysplasia: A syndrome of multiple osseous dysplasia, ear anomaly, and short stature. J. Bone Joint Surg. [Am.], *49-A*:1541, 1967.



Note the horizontal clavicles, bulge of the upper portion of the scapulae lateral to the neck, dislocated radial head with hypoplasia of capitellum, and anomalous ear lobule in this adult female. (Courtesy of R. K. Beals, University of Oregon Medical School, Portland.)





GENERALIZED GANGLIOSIDOSIS SYNDROME, TYPE I (SEVERE INFANTILE TYPE)

(Caffey's Pseudo-Hurler Syndrome, Familial Neurovisceral Lipidosis)

Coarse Facies, Joint Limitation, and Kyphosis in Early Infancy

In 1951, Caffey[1] described two neonates who had many of the features of Hurler's syndrome, but of prenatal onset. Landing, et al.[2] reported pathologic studies in similar cases showing foamy histiocytes in liver and spleen, swollen neurons, and vacuoles in the glomerular epithelium. They interpreted the storage material as a glycolipid and set forth the name "familial neurovisceral lipidosis," which was changed to "generalized gangliosidosis" by O'Brien[3] on the basis of finding elevated levels of ganglioside GM_1 in liver, spleen, and brain tissue from such a patient.

ABNORMALITIES

Growth. Growth deficiency with relatively low birth weight and severe postnatal deficit in growth.

Performance. Severe early defect in developmental performance with hypotonia, poor coordination, and later spasticity. Neuronal lipidosis with swollen neurons at necropsy.

Orofacial. Coarse features with low nasal bridge, broad nose, flaring alae nasi, frontal bossing, long philtrum, hypertrophied alveolar ridges with prominent maxilla and mild macroglossia. Hirsutism.

Eyes. Cherry-red macular spot in about one half of patients.

Skeletal. Moderate joint limitation with thick wrists, contractures at the elbows and knees, and development of claw hand. Early roentgenograms show poorly mineralized, coarsely trabeculated long bones with medullary mid-shaft broadening and a "cloak" of subperiosteal new bone formation, especially evident in the humerus. Some metaphyseal cupping and epiphyseal irregularity are usually present. With time the bones appear more like those of the Hurler syndrome, including kyphosis with anterior bullet wedging of vertebrae. Ribs are thick, legs may be bowed, and club foot may be present. Short broad hands. Kyphoscoliosis.

Viscera. Variable hepatomegaly with some foamy histiocytes. Vacuolization in glomerular epithelial cells containing swollen lysosomes.

Leukocytes. Vacuolization within cytoplasm of leukocytes and foam cells in marrow.

Urinary Excretion. Mucopolysaccharide normal or slightly elevated.

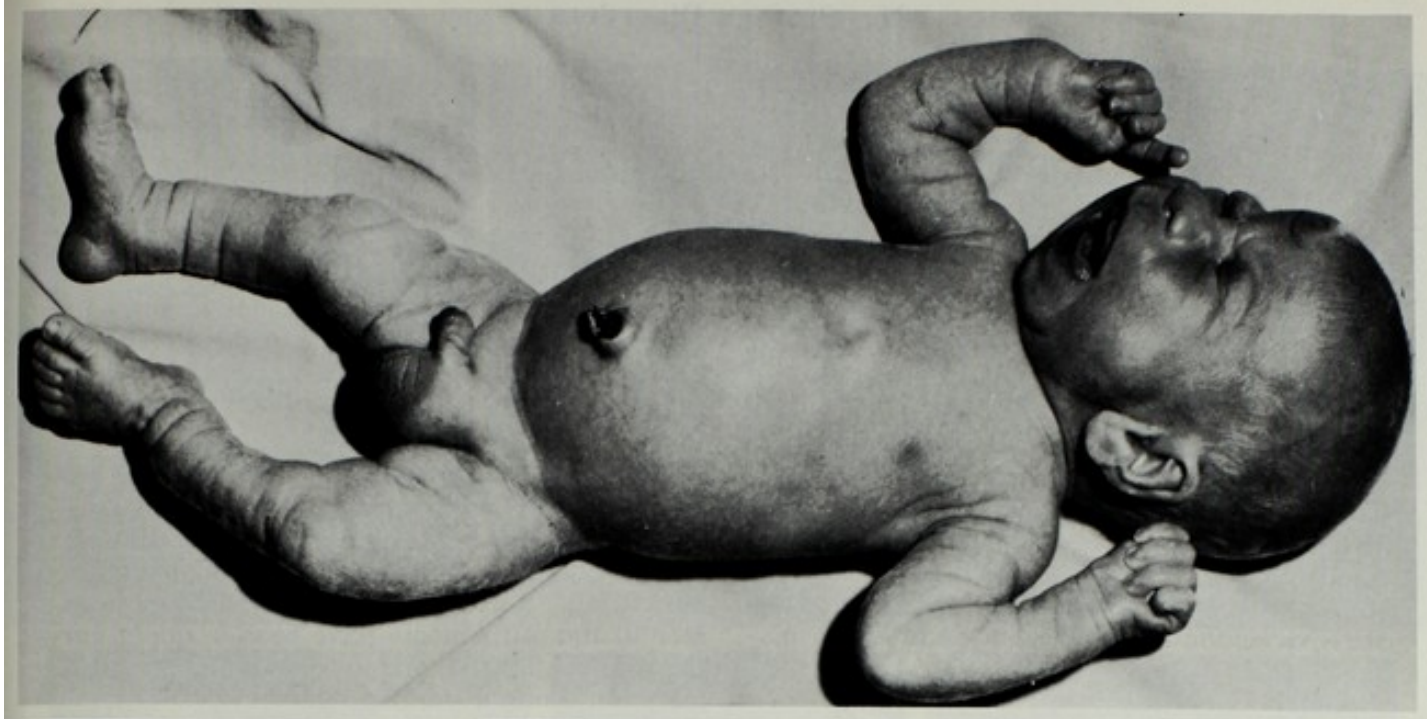
Other. Facial and peripheral edema in early infancy.

NATURAL HISTORY. Severe developmental lag with hypotonia, feeding problems with failure to thrive, and frequent infections usually culminate in death during early infancy. Deterioration of cerebral function is rapid if the patient survives the first year, leading to a decerebrate status with seizures and death prior to two years of age. The mean age of survival for 17 patients was 13.5 months, with a range from 3.5 to 25 months. No form of therapy other than life-supportive tube-feeding and antibiotic management of infections has been effective. Considering the natural history of this disorder, the author favors discussion with the parents followed by the withholding of life-supportive medical treatment if this course of management is acceptable to the parents.

ETIOLOGY. Autosomal recessive. O'Brien[3] has detected a severe deficit (one twentieth of normal) of the lysosomal enzyme β-galactosidase in liver from these patients. The presumed developmental pathology of the disease is as follows: (1) inability to cleave the terminal galactose from ganglioside and mucopolysaccharide, (2) accumulation of these products within lysosomes where they would normally be degraded, and (3) the storage disease.

REFERENCES

1. Caffey, J.: Gargoylism (Hunter-Hurler disease, dysostosis multiplex, lipochondrodystrophy); prenatal and neonatal bone lesions and their early postnatal evolution. Bull. Hosp. Joint Dis., *12*:38, 1951.
2. Landing, B. H., Silverman, F. N., Craig, J. M., Jacoby, M. D., and Chadwick, D. L.: Familial neurovisceral lipidosis. An analysis of eight cases of a syndrome previously reported as "Hurler-variant," "Pseudo-Hurler disease," and "Tay-





Two week old with x-rays of the arm, leg and thoracolumbar vertebrae. Note the coarse facies, hypertrophied alveolar ridges, broad wrists, periosteal cloaking with thin cortices, altered shape of head of humerus and femur, and hypoplastic vertebrae. (From Scott, R., et al.: J. Pediatr., *71*:357, 1967.)

Sachs disease with visceral involvement." Am. J. Dis. Child., *108*:503, 1964.

3. O'Brien, J.: Generalized gangliosidosis. J. Pediatr., *75*:167, 1969.

4. Kaback, M. M., Sloan, H. R., Sonneborn, M., and Herndon, R. M.: GM_1—Gangliosidosis type I: In-utero detection and fetal manifestations. J. Pediatr., *82*:1037, 1973.

LEROY I-CELL SYNDROME

(Mucolipidosis II)

Early Alveolar Ridge Hypertrophy, Joint Limitation, Thick Tight Skin in Early Infancy

This disorder was recognized by Leroy,[1] when he noted unusual cytoplasmic inclusions in the cultured fibroblasts of a girl who had been considered to have the Hurler syndrome, despite the fact that she did not have cloudy corneas or excessive acid mucopolysaccharide in the urine.

ABNORMALITIES

Growth. Birth weight less than 5½ pounds. Marked growth deficiency with lack of linear growth after infancy.

Performance. Slow progress from early infancy, reaching a plateau around 18 months with no apparent deterioration subsequently.

Craniofacial. High narrow forehead.
Thin eyebrows, puffy eyelids, inner epicanthic folds, clear or faintly hazy corneas.
Low nasal bridge, anteverted nostrils. Long philtrum.

Mouth. Progressive hypertrophy of alveolar ridges.

Skeletal and Joints. Moderate joint limitation in flexion, especially hips.
Dorsolumbar kyphosis.
Broadening of wrists and fingers.
X-ray findings in the later phases like those seen in children with the Hurler syndrome. In early infancy periosteal new bone formation leading to a "cloaking" of the long tubular bones is best seen in femora and humeri.

Skin. Thick, relatively tight skin during early infancy that becomes less tight as the patients become older.
Cavernous hemangiomata.

Other. Minimal hepatomegaly.
Diastasis recti.
Inguinal hernia (one case).
Systolic murmurs after one year of age.

Note. No metachromatic granules noted in leukocytes.
Urinary mucopolysaccharides normal to mildly increased.

NATURAL HISTORY. By 18 months of age most patients can sit with support and some stand with support. Smiling, early vocalization, and some other social responses develop and are maintained. Recurrent bouts of bronchitis, pneumonia, and otitis media have been frequent during early childhood, and mucous nasal discharge has been a minor problem.

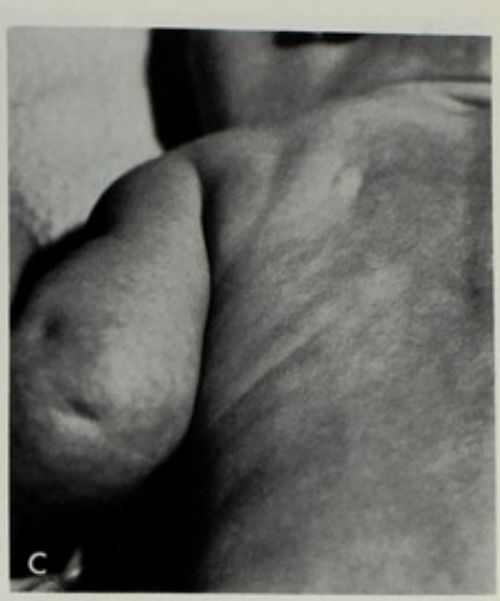
ETIOLOGY. Autosomal recessive. The material which swells the lysosomes and thereby gives rise to the cytoplasmic inclusions noted in cultured fibroblasts has not been identified. There is accumulation of acid mucopolysaccharide and glycolipids, and the optically dense granular inclusions stain with Sudan black B and para-aminosalicylic acid. The major lysosomal enzymes are depressed, suggesting a basic lysosomal membrane defect with a diffuse enzymatic leak. Further studies are in progress to more distinctly differentiate this condition from other lipomucopolysaccharidoses. Similar but less frequent cytoplasmic inclusions were noted in the fibroblast cells of the otherwise normal parents, a presumed heterozygous expression.

REFERENCES

1. Leroy, J. G., and DeMars, R. I.: Mutant enzymatic and cytological phenotypes in cultured human fibroblasts. Science, *157*:804, 1967.
2. Matalon, R., Cifonelli, J. A., Zellweger, H., and Dorfman, A.: Lipid abnormalities in a variant of the Hurler syndrome. Proc. Natl. Acad. Sci. U.S.A., *59*:1097, 1968.
3. Leroy, J. G., DeMars, R. I., and Opitz, J. M.: "I-cell" disease. The First Conference on the Clinical Delineation of Birth Defects. D. S. Bergsma, Editor. Part IV. Baltimore, Williams and Wilkins, 1969.
4. Leroy, J. G., Spranger, J. W., Feingold, M., Opitz, J. M., and Crocker, A. C.: I-Cell disease, a clinical picture. J. Pediatr., *79*:360, 1971.



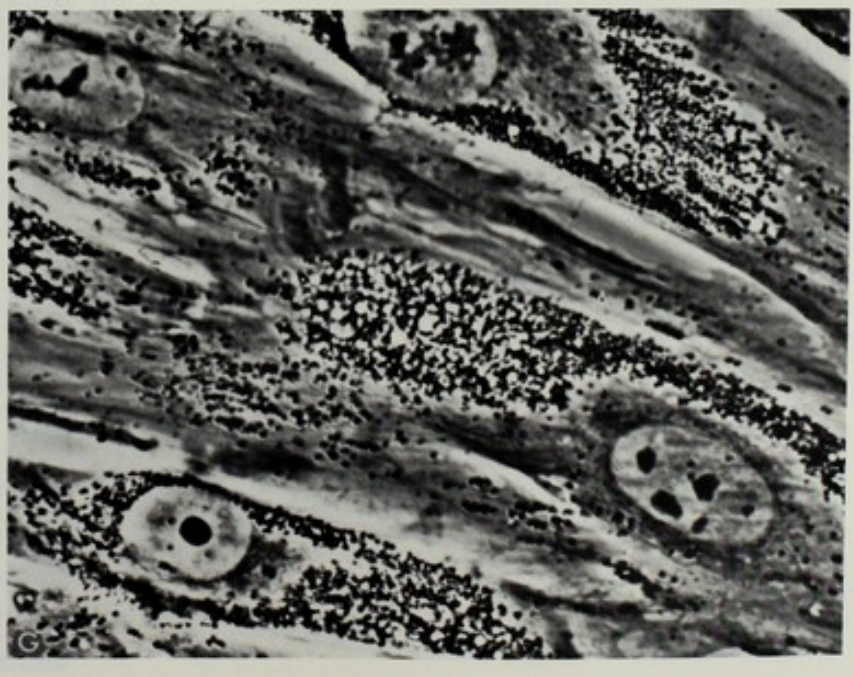












A to *D*, Five months old. Note narrow forehead, tight skin with dimpling over elbow and scapula *(C)*, and hypertrophy of alveolar ridge *(D)*.

E, Same patient at two and one half years; height age, 14 months.

F, Same patient at six years; height age, 14 months.

G, Phase contrast photo of cultured fibroblasts, showing cytoplasmic inclusions. Magnification about 700×. (From Leroy, J. G., and DeMars, R. I.: Science, *157*:804, 1967.)

HURLER SYNDROME

(Mucopolysaccharidosis I)

Coarse Facies, Stiff Joints, Mental Deficiency, Cloudy Cornea by One to Two Years

Hurler[1] set forth this entity in 1919, two years after the Hunter syndrome was described.

ABNORMALITIES[2, 3]

Growth. Deceleration of growth between six and 18 months; maximal stature 110 cm.

Performance. Grossly retarded progress at six to 12 months with failure of advancement by two to five years.

Craniofacial and Eye. Scaphocephalic macrocephaly with frontal prominence, coarse facies with full lips, flared nostrils, low nasal bridge and tendency toward hypertelorism. Inner epicanthal folds.

Hazy corneas, retinal pigmentation.

Mouth. Hypertrophied alveolar ridge and gum with small malaligned teeth. Enlarged tongue.

Skeletal and Joints. Diaphyseal broadening of short misshapen bones and joint limitation yield the claw hand and other joint deformities with more limitation of extension than flexion. Flaring of the rib cage. Kyphosis and thoracolumbar gibbus secondary to anterior vertebral wedging, short neck. J-shaped sella turcica.

Cardiac. Murmurs; cardiac failure may be due to intimal thickening in the coronary vessels or the cardiac valves.

Other. Hirsutism, hepatosplenomegaly, inguinal hernia, umbilical hernia, dislocation of hip, mucoid rhinitis, deafness.

Urinary Excretion. Dermatan sulfate and heparan sulfate.

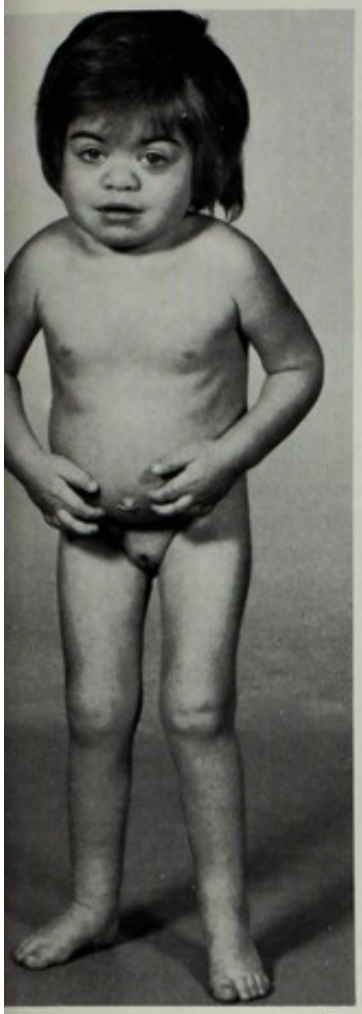
OCCASIONAL ABNORMALITIES. Hydrocephalus, presumably due to meningeal involvement. Hydrocele.

NATURAL HISTORY. Growth during the first year may actually be more rapid than usual with subsequent deterioration. Subtle changes in the facies, macrocephaly, herniae, limited hip motility, noisy breathing, and frequent respiratory infections may be evident during the first six months. Deceleration of developmental and mental progress is evident during the latter half of the first year. They are usually placid, easily manageable, and often loveable. Death usually occurs in childhood secondary to respiratory or cardiac complications, and survival past ten years of age is unusual.

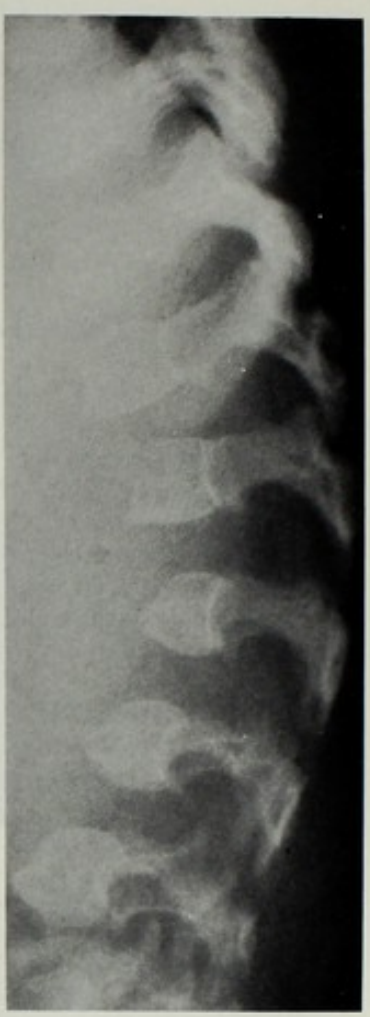
ETIOLOGY. Autosomal recessive, due to α-iduronidase deficiency. The asymptomatic carriers may be recognized by abnormal lysosomal accumulation of mucopolysaccharide in their cultured fibroblast cells, a phenomenon which is more striking in the homozygote.

REFERENCES

1. Hurler, G.: Ueber einen Typ multipler Abartungen, vorwiegend am Skelettsystem. Z. Kinderheilkhd., *24*:220, 1919.
2. McKusick, V.: Heritable Disorders of Connective Tissue, 4th ed. St. Louis, C. V. Mosby Co., 1972.
3. Leroy, J. G., and Crocker, A. C.: Clinical definition of the Hurler-Hunter phenotypes. A review of 50 patients. Am. J. Dis. Child., *112*:518, 1966.
4. Spranger, J.: The systemic mucopolysaccharidoses. *In* Ergebnisse del Inneren Medizin und Kinderheilkunde. New York, Springer-Verlag, 1972.











A, Two year old who sat at one year and walked at 21 months. Height age at six months was ten months; at one year, 16 months; and at two years, two years.

B, Broad irregular bone, especially at metaphyses. Thoracic and lumbar vertebrae are short with anterior wedging.

C, Five year old with height age of three years.

PSEUDO-HURLER POLYDYSTROPHY SYNDROME

(Mucolipidosis III)

Coarse Facies, Stiff Joints by Two to Four Years, No Mucopolysaccharidiuria

Recognized by Maroteaux and Lamy[1] in 1966, more than 15 cases have subsequently been reported.[2-4] Clinically the disorder is of milder degree than in the Hurler syndrome and the patients do not have hepatosplenomegaly or mucopolysaccharidiuria. About 18 patients have been recognized.

ABNORMALITIES. Onset usually appreciated at 1 to 4 years.

Growth. Decreasing growth rate in early childhood.

Performance. Mild mental deficiency, I.Q. 64 to 85.

Facies. Development of mildly coarse facies by six years.

Eyes. Mild corneal opacities, evident by slit lamp, by six to eight years.

Joint. Stiffness, especially in hands, elbows, shoulders, knees.

Skeletal. Mild platyspondyly, flaring iliac wings, flattening of femoral epiphyses, changes in hands.

Cardiac. Aortic valve disease, often with regurgitation.

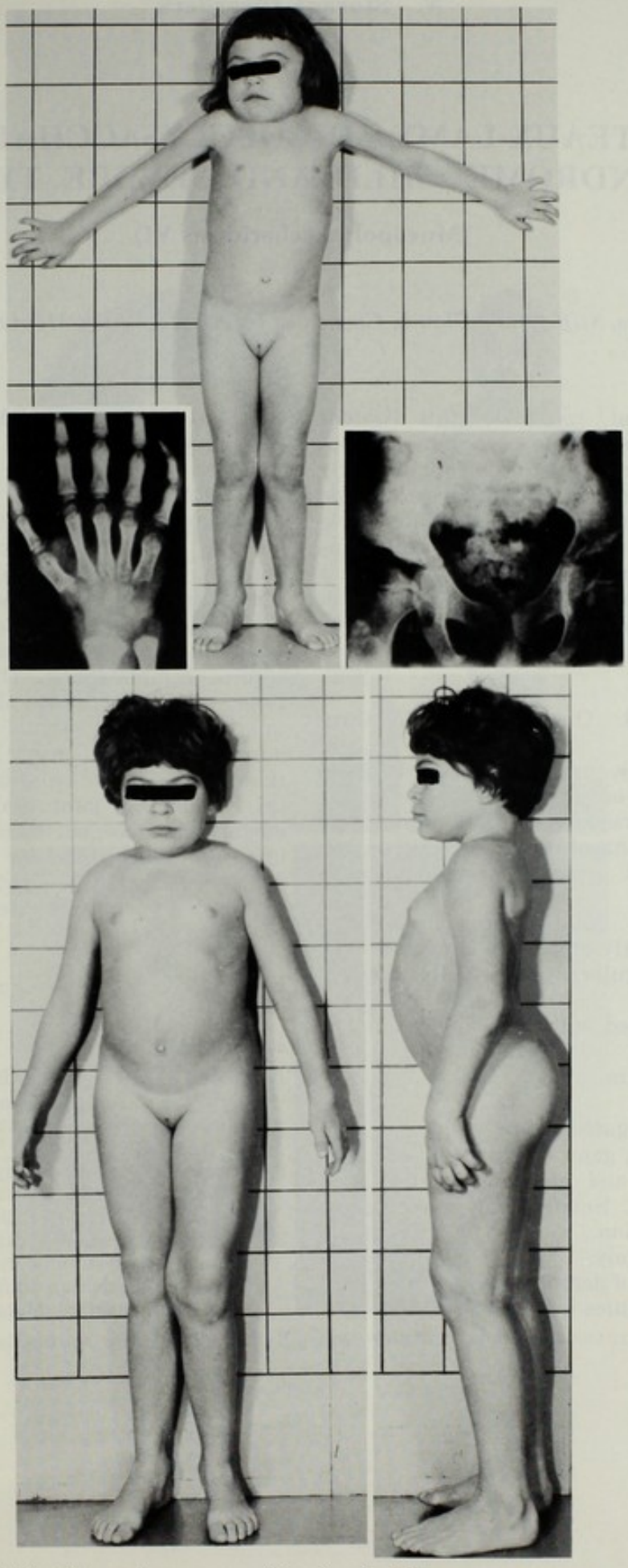
Other. Inguinal hernia. Acne.

NATURAL HISTORY. Stiffness of joints usually becomes evident by one to four years of age. Carpal tunnel compression is a potential complication. Mild to moderate deterioration of central nervous system function.

ETIOLOGY. Autosomal recessive inheritance. Marrow plasma cells show vacuolated plasma cells with swollen lysosomes, but there is no mucopolysaccharidiuria. Lysosomal enzyme values may be elevated in the serum.

REFERENCES

1. Maroteaux, P., and Lamy, M.: La pseudo-polydystrophie de Hurler. Presse Med., *74*:2889, 1966.
2. Scott, C. I., Jr., and Grossman, M. S.: Pseudo-Hurler polydystrophy. Birth Defects, *4(5)*:349, 1969.
3. McKusick, V. A.: Heritable Disorders of Connective Tissue, 4th ed. St. Louis, C. V. Mosby Co., 1972, p. 652.
4. Thomas, G. H., Taylor, H. A., Reynolds, L. W., and Miller, C. S.: Mucolipidosis III (pseudo-Hurler Polydystrophy): Multiple lysosomal enzyme abnormalities in serum and cultured fibroblast cells. Pediatr. Res., *7*:751, 1973.



Above, Six year old girl with roentgenograms of hand and pelvis.

Below, Early adolescent girl showing mild facial coarsening, joint contractures, and lumbar lordosis. (Courtesy of C. Scott, University of Texas. From Scott, C. I., Jr., and Grossman, M. S.: Birth Defects, *4*:349, 1969.)

MAROTEAUX-LAMY MUCOPOLYSACCHARIDOSIS SYNDROME (MILD AND SEVERE TYPES)

(Mucopolysaccharidosis VI)

Coarse Facies, Stiff Joints, Cloudy Cornea in Infancy, Without Mental Deterioration

Maroteaux, et al.[1] recognized this disorder as being distinct from Hurler's syndrome, in that mental deterioration did *not* occur during early childhood and the only mucopolysaccharide found in the urine was dermatan sulfate. However, Fallis, et al.[3] reported heparan sulfate as well as dermatan sulfate in the urine of such a patient. Two clinical subtypes have been indicated, one with a slow and milder course and the other with a rapid and severe course.

ABNORMALITIES. Onset by one to three years of age.

Growth. Deficiency, usually evident between two and three years.

Craniofacial. Coarse facies with large nose and thick lips. Low nasal bridge.

Eye. Fine corneal opacity. Cornea may be thick, large.

Skeletal and Joints. Mild stiffness of joints.
Metaphyses slightly broad and irregular.
Epiphyseal irregularity, especially femoral epiphysis.
Vertebrae flattened with anterior wedging of T-12 and L-1.
Prominent sternum.
Ribs broad.
Sella turcica elongated.
Lumbar kyphosis, genu valgum.

Other. Umbilical and inguinal herniae. Skin thick and tight. Small widely spaced teeth with late eruption.
Hepatosplenomegaly.
Varying degrees of deafness.
Cytoplasmic granules in leukocytes.

OCCASIONAL ABNORMALITIES. Macroglossia. Macrocephaly.

NATURAL HISTORY. Macrocephaly, frequent upper respiratory infections and diarrhea, herniae and limitation of knee, hip, and elbow movement may be present in infancy. Thereafter the two clinical subtypes diverge. Those with the mild slow course usually survive until the second to third decade and succumb to cardiac complications. Those with the severe type rapidly deteriorate physically and by three to six years have serious deformity. The age of onset of growth deficiency is usually a little later than in the Hurler's disease; the extent of skeletal broadening, joint limitation, hepatosplenomegaly, and corneal opacification is generally less than with Hurler's disease, and mental deficiency has not been noted during childhood. The data on prognosis after ten years of age are presently inadequate.

ETIOLOGY. Presumed autosomal recessive.

REFERENCES

1. Maroteaux, P., Levêque, B., Marie, J., and Lamy, M.: Une nouvelle dysostose avec élimination urinaire de chondroitine-sulfate B. Presse Med., *71*:1849, 1963.
2. Maroteaux, P., and Lamy, M.: Hurler's disease, Morquio's disease, and related mucopolysaccharidoses. J. Pediatr., *67*:312, 1965.
3. Fallis, N., Barnes, F. L., II, and di Ferrante, N.: A case of polydystrophic dwarfism with urinary excretion of dermatan sulfate and heparan sulfate. J. Clin. Endocrinol. Metab., *28*:26, 1968.



Older boy, short of stature, with normal intelligence. (Courtesy of P. Maroteaux, Hôpital des Enfants-Malades, Paris.)

HUNTER SYNDROME (JUVENILE AND LATE TYPES)

(Mucopolysaccharidosis II)

Coarse Facies, Growth Deficiency, Stiff Joints by Two to Four Years, Clear Cornea

Hunter[1] described this condition in 1917 in two brothers. Two clinical types have been distinguished, the juvenile one being the more severe.

ABNORMALITIES.[2,3] Onset around two to four years.

Growth. Growth deficiency, onset one to four years. Adult height 120 to 150 cm.

Performance. Juvenile type: Mental and neurologic deterioration around two to five years of age toward severe mental deficiency with aggressive hyperactive behavior and spasticity. Late type: Mental deficiency variable, usually mild.

Craniofacial. Coarsening of facial features, full lips. Macrocephaly.

Joint and Skeletal. Stiff partial contracture of joints, claw hand. Broadening of bone.

Other. Hepatosplenomegaly, hypertrichosis, inguinal hernias, mucoid nasal discharge, progressive deafness. Delayed tooth eruption.

Urinary Excretion. Dermatan sulfate and heparan sulfate.

OCCASIONAL ABNORMALITIES. Diarrhea, nodular skin lesions over scapular area and on arms, kyphosis, pes cavus, osteoarthritis of head of femur, retinal pigmentation, congestive heart failure, coronary occlusion.

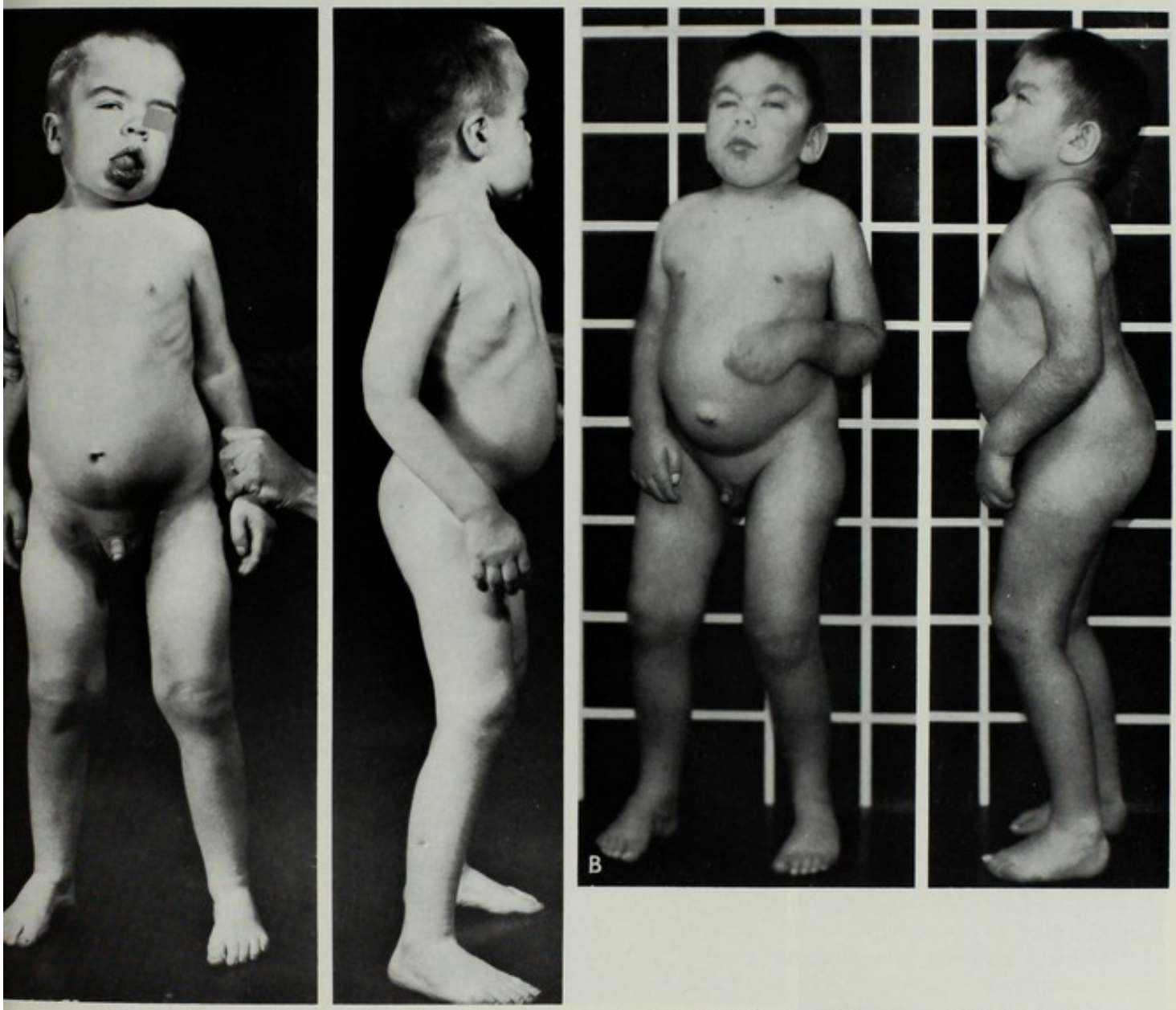
IMPORTANT DIFFERENCES IN CONTRAST TO THE HURLER SYNDROME. (1) Clear corneas. (2) No gibbus. (3) No affected females. (4) More gradual onset of features.

NATURAL HISTORY. Gradual decline in growth rate from two to six years. Deafness frequently is evident by two to three years. Cardiac complications not uncommonly lead to death prior to 20 years; however, survival to 60 years has been recorded. The more severe juvenile-type patients tend to die earlier, between four and 14 years of age.

ETIOLOGY. X-linked, with no overt expression in the heterozygous female who may be recognized by the fact that cultured fibroblasts show cytoplasmic accumulation of mucopolysaccharide, though to a lesser extent than those of the hemizygous male.

REFERENCES

1. Hunter, C.: A rare disease in two brothers. Proc. R. Soc. Med., *10*:104, 1917.
2. McKusick, V.: Heritable Disorders of Connective Tissue, 4th ed. St. Louis, C. V. Mosby Co., 1972, p. 346
3. Leroy, J. G., and Crocker, A. C.: Clinical definition of the Hurler-Hunter phenotypes. A review of 50 patients. Am. J. Dis. Child., *112*:518, 1966.



A, Nine and one half year old with height age of seven and two thirds years. (Courtesy of A. C. Crocker, Boston Children's Hospital.)

B, Thirteen and one half year old with height age of seven years.

MORQUIO SYNDROME

(Mucopolysaccharidosis IV)

Onset at One to Three Years of Age, Mild Coarse Facies, Severe Kyphosis and Knock Knee, Cloudy Cornea

Mistakenly interpreted by Osler[1] in 1898, this condition was described by Morquio[2] in 1929; it was only recently recognized as a mucopolysaccharidosis.[3]

ABNORMALITIES. Onset between one and three years.

Growth. Severe limitation with cessation by latter childhood. Adult stature 82 to 115 cm.

Craniofacial. Mild coarsening of facial features with broad mouth and short anteverted nose.

Eye. Cloudy cornea evident by slit lamp examination, usually after five to ten years of age.

Skeletal and Joint. Marked platyspondyly with vertebrae changing to ovaloid, ovaloid with anterior projection, to flattened form with short neck and trunk plus kyphoscoliosis.

Early flaring of rib cage progressing to bulging sternum.

Short curved long bones with irregular tubulation, widened metaphyses, abnormal femoral neck, flattening of femoral head, knock knee with medial spur of tibial metaphysis, conical bases of widened metacarpals, irregular epiphyseal form, osteoporosis. Short stubby hands.

Joint laxity, most evident at wrist and small joints and joint restriction in some of larger joints, especially the hips.

Mouth. Widely spaced teeth with thin enamel which tends to become greyish in color.

Cardiac. Late onset of aortic regurgitation.

Other. Hearing loss. Inguinal hernia. Hepatomegaly.

Urinary Excretion. Keratosulfate.

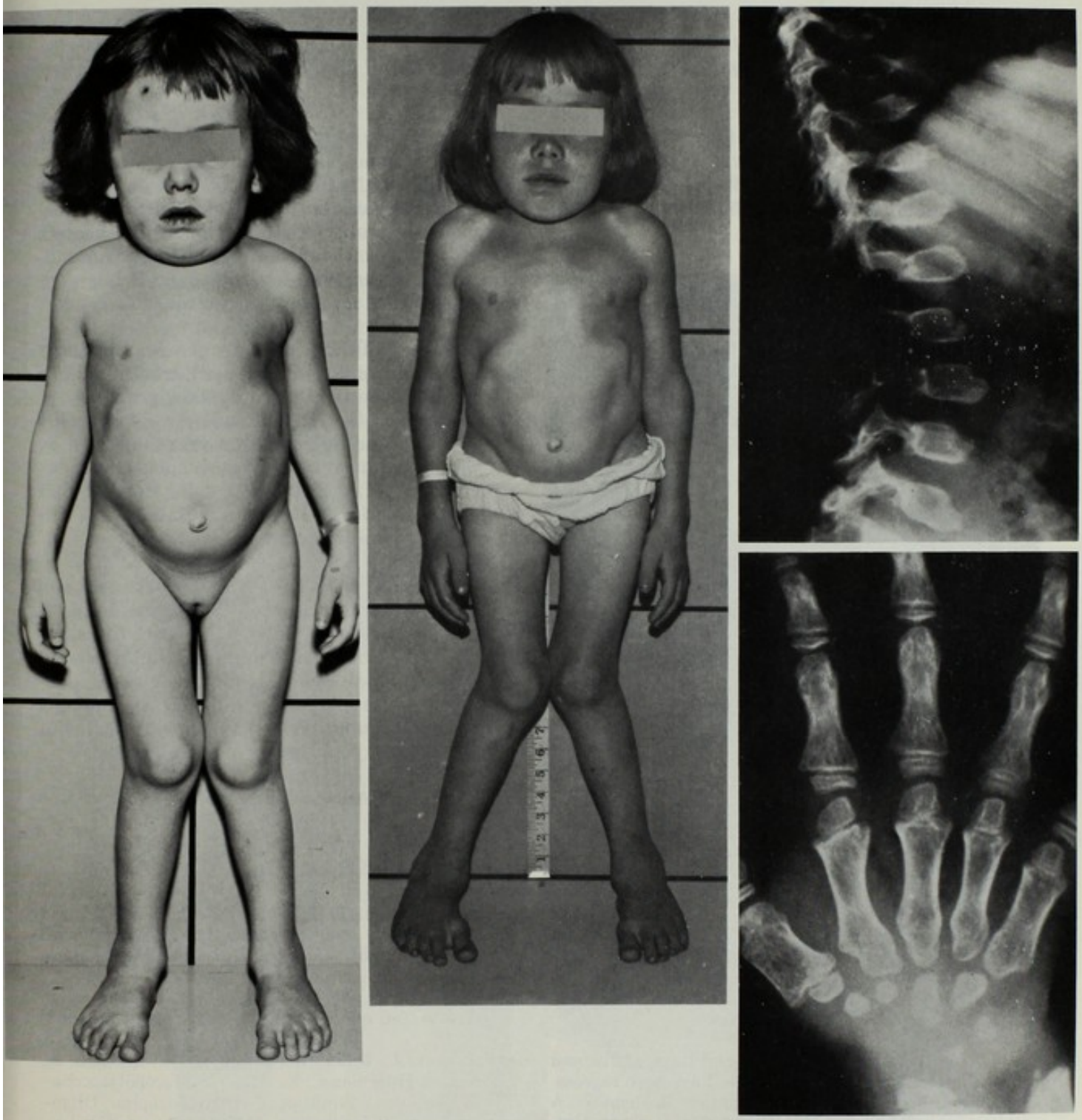
OCCASIONAL ABNORMALITIES. Macrocephaly, mental deficiency.

NATURAL HISTORY. The earliest recognized indications of the disease have been flaring of the lower rib cage, prominent sternum, frequent upper respiratory infections, including otitis media, herniae, and growth deficiency; all becoming evident by 18 months to two years of age. Severe defect of vertebrae may result in cord compression or respiratory insufficiency. These and cardiac complications may result in death prior to 20 years, although later survival has occurred. Mentality is usually normal.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Osler, W.: Sporadic cretinism in America. Trans. Cong. Am. Phys., *4*:169, 1897.
2. Morquio, L.: Sur une forme de dystrophie osseuse familiale. Arch. Med. Enf., *32*:129, 1929.
3. Robins, M. M., Stevens, H. F., and Linker, A.: Morquio's disease: an abnormality of mucopolysaccharide metabolism. J. Pediatr., *62*:881, 1963.
4. Langer, L. O., and Carey, L. S.: The roentgenographic features of the ks mucopolysaccharidosis of Morquio (Morquio-Brailsford's disease). Am. J. Roentgenol. Radium Ther. Nucl. Med., *97*:1, 1966.
5. Linker, A., Evans, L. R., and Langer, L. O.: Morquio's disease and mucopolysaccharide excretion. J. Pediatr., *77*:1039, 1970.



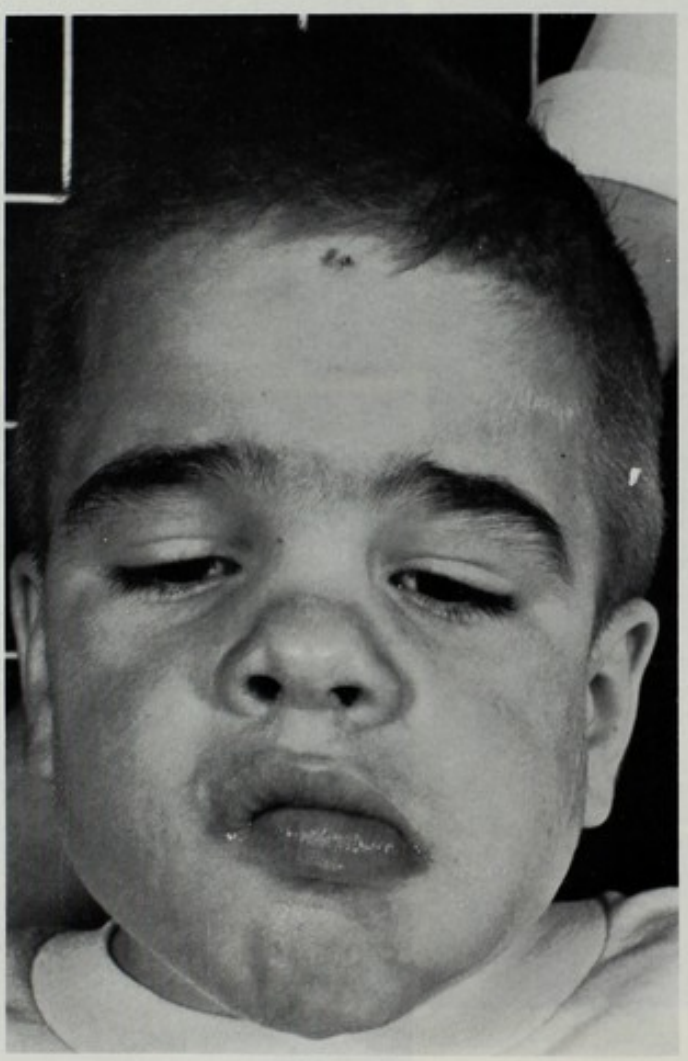
Left, Three and one half years; height age, two and three fourths years. *Center,* Same patient at seven years; height age, two and three fourths years. *Right,* X-rays of patient at seven years. (From Robins, M. M., et al.: J. Pediatr., *62*:881, 1963.)

SANFILIPPO SYNDROME, TYPES A AND B

(Mucopolysaccharidosis VII)

Mild Coarse Facies, Mild Stiff Joints, Mental Deficiency

This clinical disorder was recognized by Sanfilippo, et al.[1] in 1963 and appears to be the most common mucopolysaccharidosis disorder.



A seven year old with the height age of five and three fourths years. His capabilities have been regressing and his present intelligence quotient is about 50. A sibling is similarly affected. (Courtesy of R. Scott, University of Washington Medical School.)

The excess mucopolysaccharide urinary excretion is heparan sulfate alone. These individuals usually have clear corneas. Two clinically indistinguishable subtypes have been delineated: type A is due to a deficiency of the heparan sulfate sulfatase enzyme whereas type B has deficiency of alpha acetyl glucosaminidase.

ABNORMALITIES. Onset in early childhood.
Growth. Normal to accelerated growth for one to three years followed by slow growth.
Performance. Slowing mental development by one and one half to three years followed by deterioration including gait, speech, and behavior.
Urinary Excretion. Heparan sulfate.
Other. Variable hepatomegaly.

NATURAL HISTORY. Sleep disturbances and frequent upper respiratory infections may be early evidence of the disorder, prior to the slowing of growth and mental deterioration. Unfortunately the usual result is severe mental deficiency in a strong, often difficult to manage, individual. Compatible with long survival, but many die by 10 to 20 years of pneumonia.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. Sanfilippo, S. J., Podosin, R., Langer, L. O., Jr., and Good, R. A.: Mental retardation associated with acid mucopolysaccharidosis (heparitin sulfate type). J. Pediatr., *63*:837, 1963.
2. McKusick, V.: Heritable Disorders of Connective Tissue. 3rd ed. St. Louis, C. V. Mosby Co., 1966, p. 357.
3. Spranger, J., Teller, W., Kosenow, W., Murken, J., Echert-Husemann, E.: Die HS-Mucopolysaccharidose von Sanfilippo (Polydystrophe Oligophrenie). Bericht über 10 Patienten. Z. Kinderheilkhd., *101*:71, 1967.

SCHEIE SYNDROME

(Mucopolysaccharidosis V)

Broad Mouth with Full Lips, Early Corneal Opacity, Normal Mentality

This disorder was originally described by Scheie, et al.[1] in 1962.

ABNORMALITIES[1, 2]

General. Little, if any, impairment of intelligence.

Facies. Broad mouth with full lips by five to eight years of age. Mandibular prognathism.

Cornea. Early clouding of cornea, becoming most dense in periphery.

Limbs. Joint limitation leading to claw hand, small carpal bones, femoral head dysplasia. Hands and feet broad and short.

Cardiac. Aortic valvular defect.

Other. Body hirsutism. Retinal pigmentation. Inguinal, umbilical herniae. Short neck.

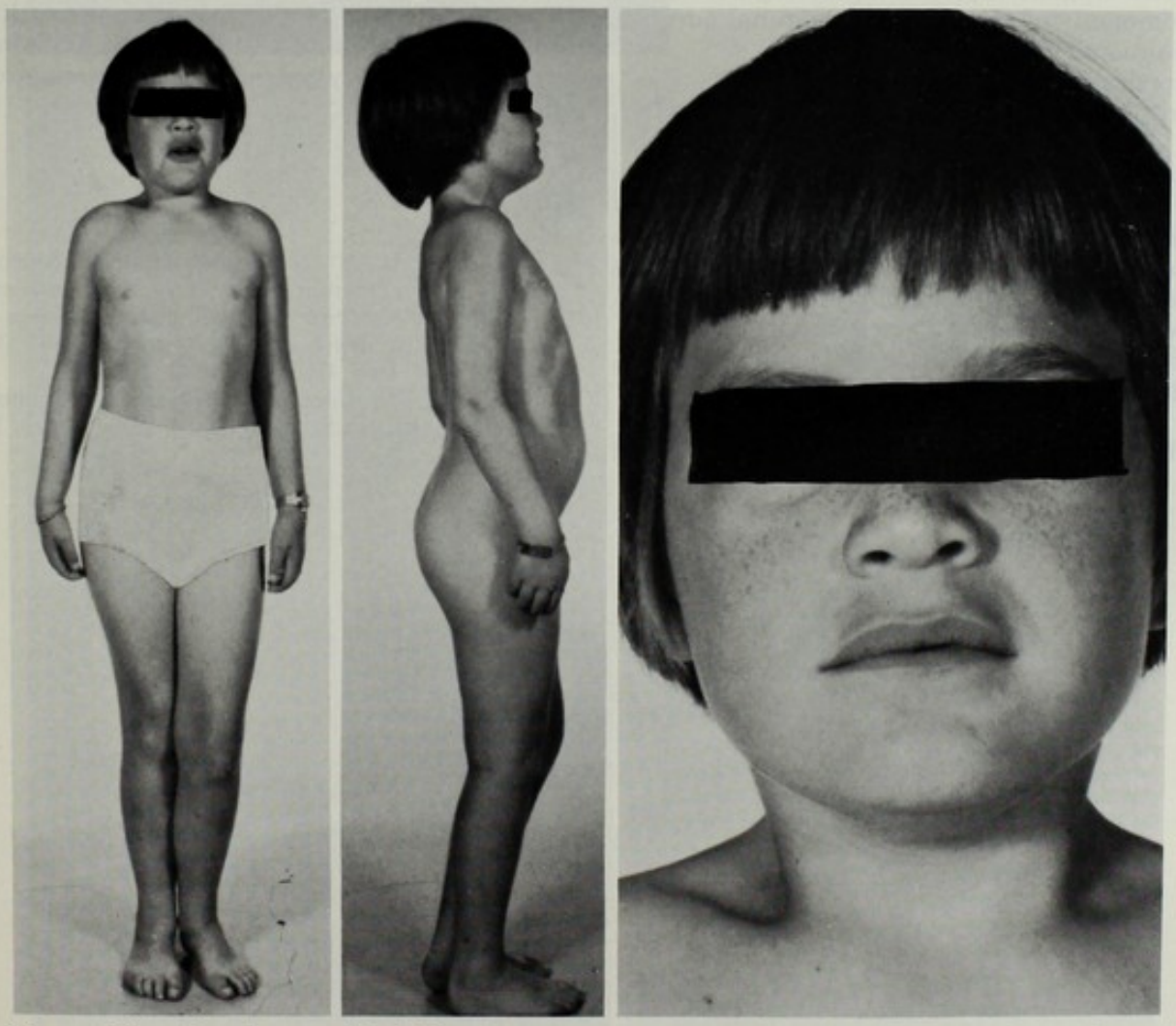
Urinary Excretion. Proportionately more dermatan sulfate than usual.

OCCASIONAL ABNORMALITIES. Carpal tunnel narrowing may cause median nerve compression. Psychosis and possible mental deterioration may occur. Mild impairment of growth. Hearing loss. Hepatomegaly. Macroglossia. Glaucoma, myopia.

ETIOLOGY. Autosomal recessive, with excess urinary excretion of dermatan sulfate.

REFERENCES

1. Scheie, H. G., Hambrick, G. W., Jr., and Barness, L. A.: A newly recognized forme fruste of Hurler's disease (gargoylism). Am. J. Ophthalmol., *53*:753, 1962.
2. Emerit, I., Maroteaux, P., and Vernant, P.: Deux observations de mucopolysaccharidose avec atteinte cardio-vasculaire. Arch. Fr. Pediatr., *23*:1075, 1966.



Nine and three fourths year old with height age of nine years and I.Q. of 102. Mild to moderate limitation of shoulder, elbow, and hand movement. Mild corneal opacity. (Courtesy of R. Scott, University of Washington.)

MARFAN SYNDROME

Arachnodactyly with Hyperextensibility, Lens Subluxation, Aortic Dilatation

Described as dolichostenomelia in the initial report of Marfan,[1] this disorder has been extensively studied and recognized as a connective tissue disorder by McKusick.[2]

ABNORMALITIES[2]

Skeletal. Tendency toward tall stature with long slim limbs, little subcutaneous fat, and muscle hypotonia.
Joint laxity with scoliosis (60 per cent) and kyphosis.
Pectus excavatum or carinatum.
Narrow facies with narrow palate.

Eye. Lens subluxation, usually upward, with defect in suspensory ligament.
Myopia. Bluish sclerae.

Cardiovascular. Dilatation with or without dissecting aneurysm of ascending aorta, less commonly of thoracic or abdominal aorta or pulmonary artery.
Secondary aortic regurgitation.

Other. Inguinal, femoral hernias.

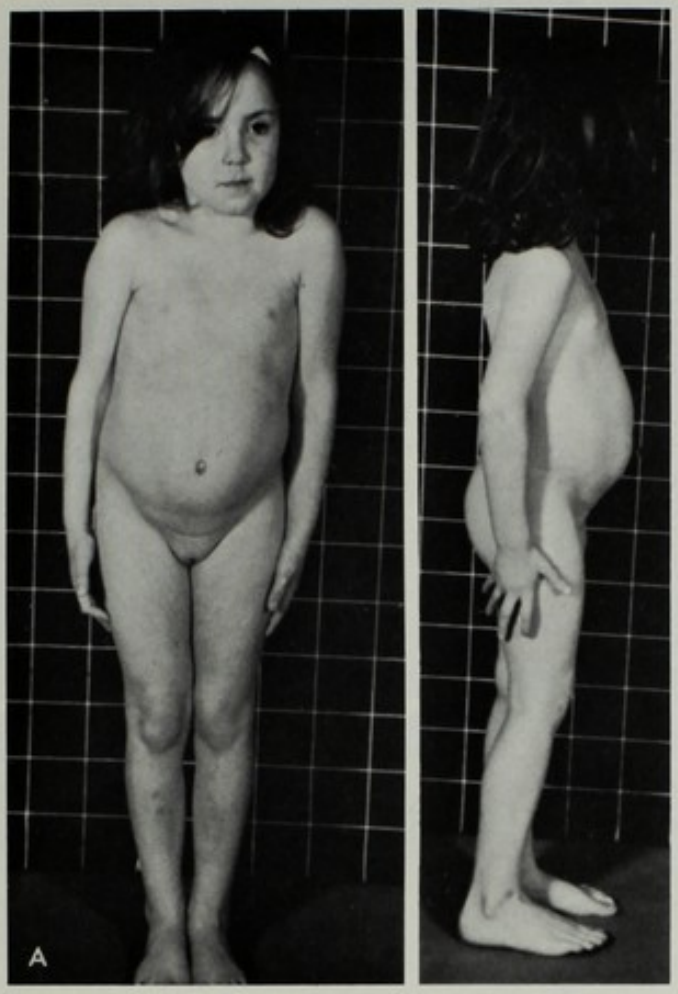
OCCASIONAL ABNORMALITIES. Large ears, retinal detachment, striae in pectoral or deltoid area, diaphragmatic hernia, pulmonary malformation contributing toward spontaneous pneumothorax and/or emphysema with an increased susceptibility to respiratory infection. Hemivertebrae, colobomata of iris, cleft palate, incomplete rotation of colon.

NATURAL HISTORY. During childhood and adolescence special care should be devoted toward prevention of scoliosis. The serious vascular complications may develop anytime from fetal life through old age and are the chief cause of death. Secondary glaucoma may occur, especially when the lens dislocates into the anterior chamber of the eye. The mean age of survival is 43 for men and 46 for women. These individuals are of normal intelligence.

ETIOLOGY. Autosomal dominant with sufficiently wide variability in expression that diagnosis is often tenuous in sporadic nonfamilial cases. Cases occur without ectopia lentis and without pronounced arachnodactyly. The basic defect in connective tissue has not been determined; however, accumulation of mucopolysaccharide has been noted within cells of the aorta from an affected individual, and the cultured fibroblast cells from individuals with the Marfan syndrome show cytoplasmic metachromatic inclusion.

REFERENCES

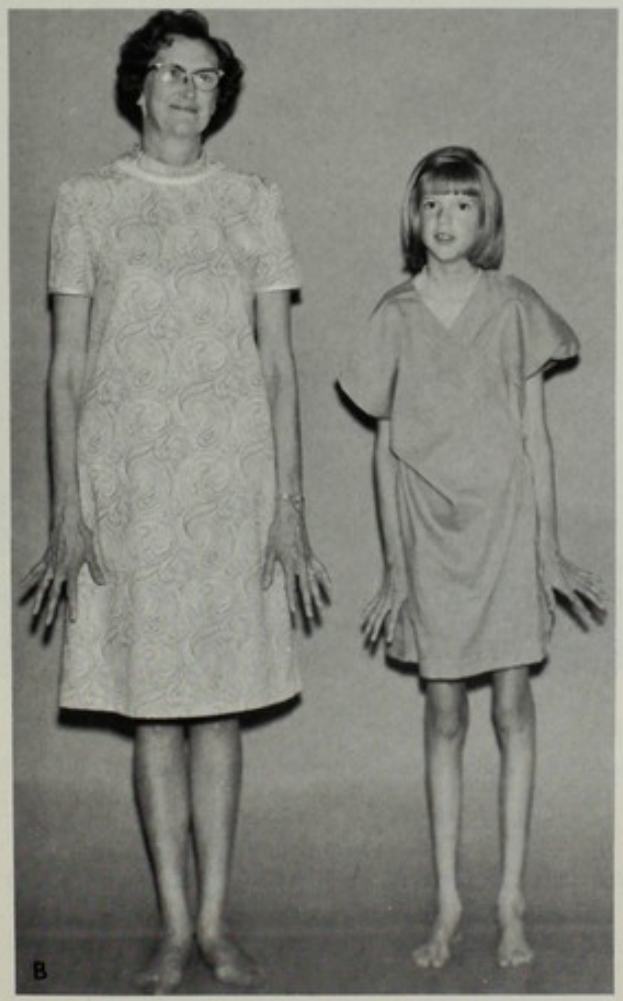
1. Marfan, A. B.: Un cas de déformation congénitale des quatre membres plus prononcée aux extrémites charactérisée par l'allongement des os avec un certain degré d'amincissement. Bull. Mem. Soc. Med. Hop. (Paris), *13*:220, 1896.
2. McKusick, V.: Heritable Disorders of Connective Tissue, 3rd ed. St. Louis, C. V. Mosby Co., 1966, p. 38.

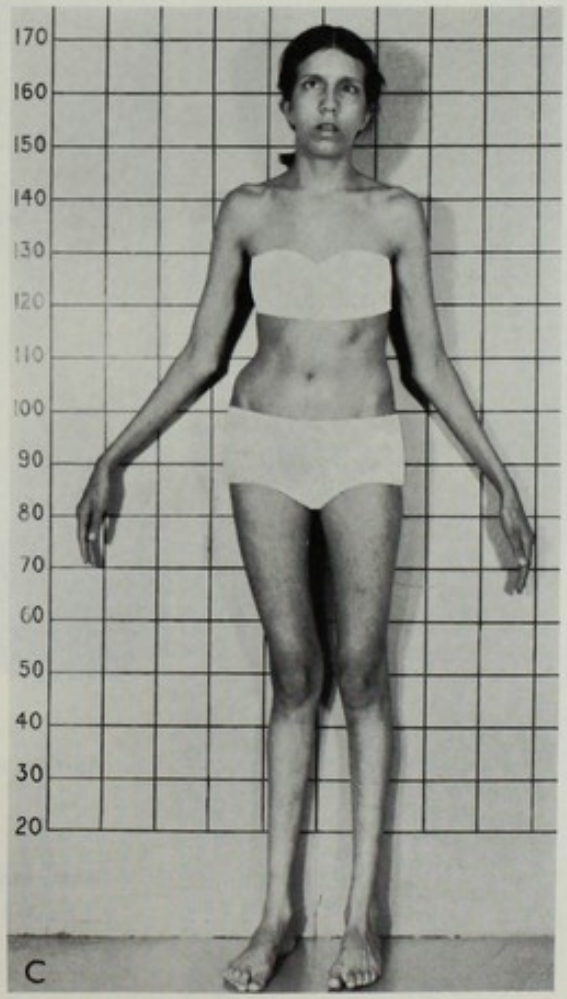


A, Three and one half year old, with height age of five years, who has lens dislocation, mild arachnodactyly of the hands and feet, unusually soft skin, and narrow palate. The family history of the Marfan syndrome in the mother and grandfather tend to confirm the diagnosis in this case.

B, Nine and one fourth year old girl with height age of twelve and one fourth years and her mother. Both have arachnodactyly, but only the mother has dislocation of the lenses.

C, Sixteen year old with arachnodactyly, hyperextensible hands and knees, limitation of extension at elbow, scoliosis, systolic and diastolic murmurs, superiorly dislocated lenses, glaucoma, and retinal detachments despite numerous surgical procedures. She represents a fresh mutation, no other family members being affected. (Courtesy of Drs. Victor McKusick and Judith Hall, the Johns Hopkins Hospital.)





CONTRACTURAL ARACHNODACTYLY SYNDROME

(Beals Syndrome)

Joint Contractures, Arachnodactyly, "Crumpled" Ear

Beals and Hecht[1, 2] described this syndrome in 1971. They found 11 probable past reports of the same entity, including the original Marfan report.

ABNORMALITIES

Limbs. Long slim limbs (dolichostenomelia) with arachnodactyly. Joint contractures, especially knees, elbows, and hands.

Other Skeletal. Kyphoscoliosis, relatively short neck.

Ear. "Crumpled" appearance with poorly defined concha and prominent crura from the root of the helix.

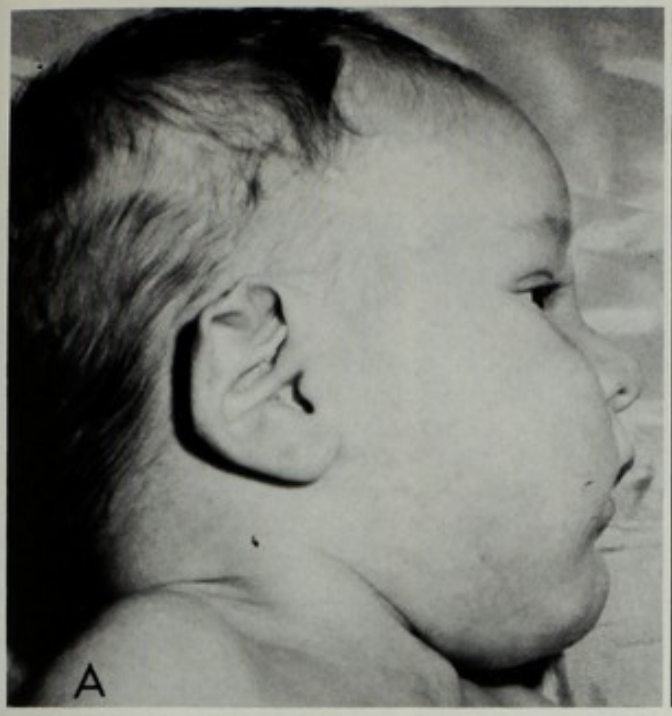
Occasional. Micrognathia.

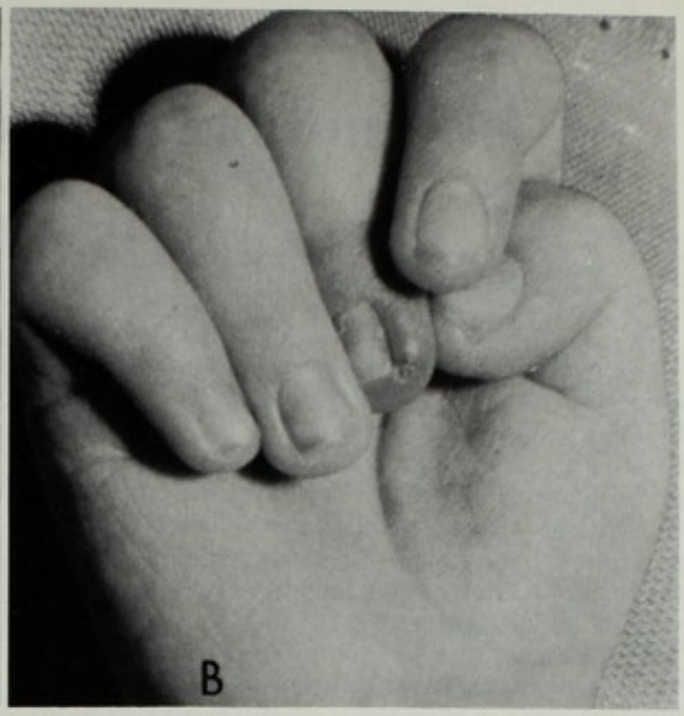
NATURAL HISTORY. There tends to be gradual improvement in the joint limitations but the scoliosis may be progressive.

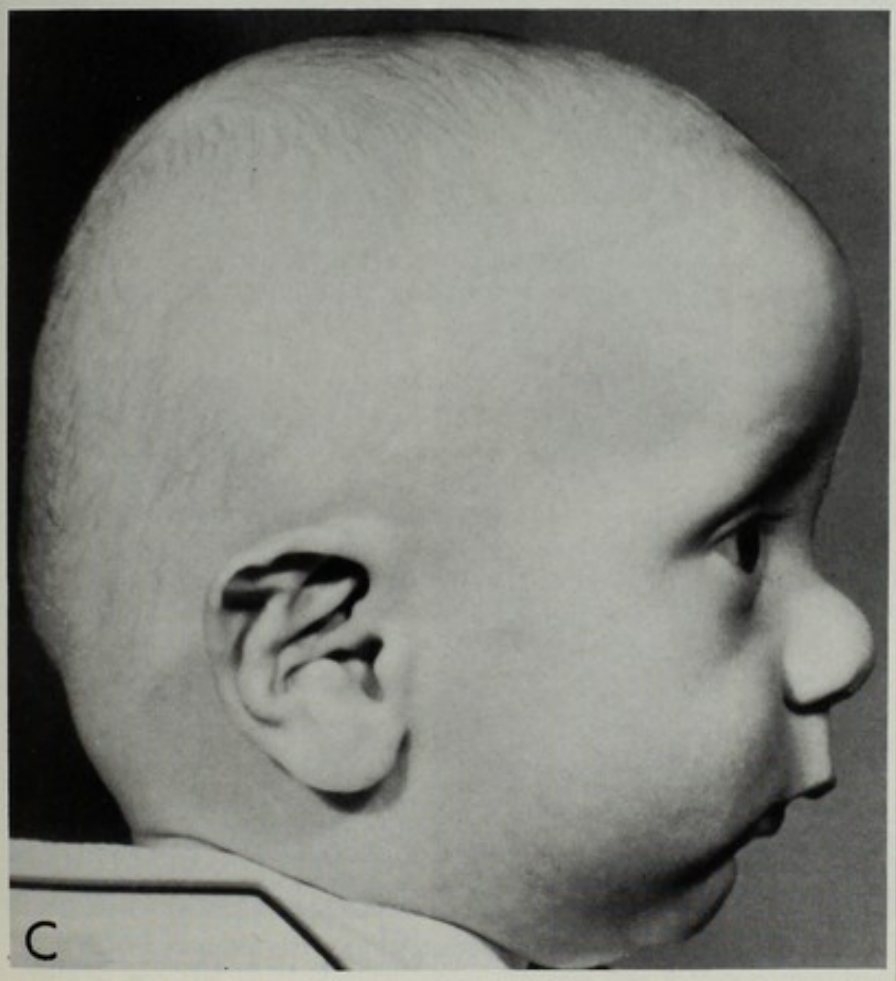
ETIOLOGY. Autosomal dominant inheritance.

REFERENCES

1. Beals, R. K., and Hecht, F.: Delineation of another heritable disorder of connective tissue. J. Bone Joint Surg. [Am.], *53*:987, 1971.
2. Hecht, F., and Beals, R. K.: "New" syndrome of congenital contractural arachnodactyly originally described by Marfan in 1896. Pediatrics, *49*:574, 1972.









A and *B*, Infant showing "crumpled" ear and aberrant position of contracted fingers.

C, Note similar appearance of ear to that in *A*.

D, Six year old sibling of infant in *C*.

(*C* and *D* from Beals, R. K., and Hecht, F.: J. Bone Joint Surg. [Am.], *53*:987, 1971.)

HOMOCYSTINURIA SYNDROME

Subluxation of Lens, Malar Flush, Osteoporosis

Urinary amino acid screening of mentally defective patients resulted in the independent discovery of this entity by Carson, et al.[1] and Gerritsen and Waisman[2] in 1963. Finkelstein[3] and coworkers found a lack of cystathionine synthetase activity in the liver of affected individuals, and this enzyme defect apparently leads to the accumulation of homocystine and methionine with a deficiency of cystathionine and cystine. The more appropriate name for the condition would therefore be cystathionine synthetase deficiency. This inborn error often results in mental defect as well as defective development in blood vessels and of connective tissues, resembling Marfan's syndrome in the latter regard.

ABNORMALITIES

General. Mental defect in 58 per cent of 38 cases.[5]

Eye. Subluxation, usually downward, of the lens by the age of ten years, the earliest instance noted being two years. Myopia.

Skeletal. Slim skeletal build resembling arachnodactyly with pectus excavatum or carinatum, genu valgum, pes cavus, everted feet with or without kyphoscoliosis. Osteoporosis.

Vasculature. Medial degeneration of aorta and elastic arteries with intimal hyperplasia and fibrosis leading to pads and ridges within the vessels. Both arterial and venous thromboses are frequent.

Skin. Malar flush with tendency to patchy erythematous blotches elsewhere.

Hair. Tends to be fine, sparse, dry, and light in color.

OCCASIONAL ABNORMALITIES. Cataracts, glaucoma, optic atrophy, cystic retinal degeneration or detachment, irregular crowded teeth, high arched palate, hernias, and hepatomegaly with fatty liver.

NATURAL HISTORY. Seizures with onset from six months to five years of age have been noted, and the electroencephalographic pattern is usually abnormal. Excessive nervousness may be a feature, occasionally with schizophrenic behavior. Neurologic defect, especially spasticity, may be present and is often asymmetrical—presumably the consequence of vascular thrombosis which can be arterial or venous and not infrequently involves the coronary artery. Venipuncture or surgical procedures may be followed by excessive vascular thrombosis and should be avoided when possible. Thromboembolic phenomena constitute the most life-threatening feature of this disease. Another problem, osteoporosis, frequently leads to partial collapse of vertebrae, and there is an increased likelihood of fractures.

Failure to thrive has been a feature of some cases with severe mental defect. However, normal to tall stature is the more usual growth pattern.

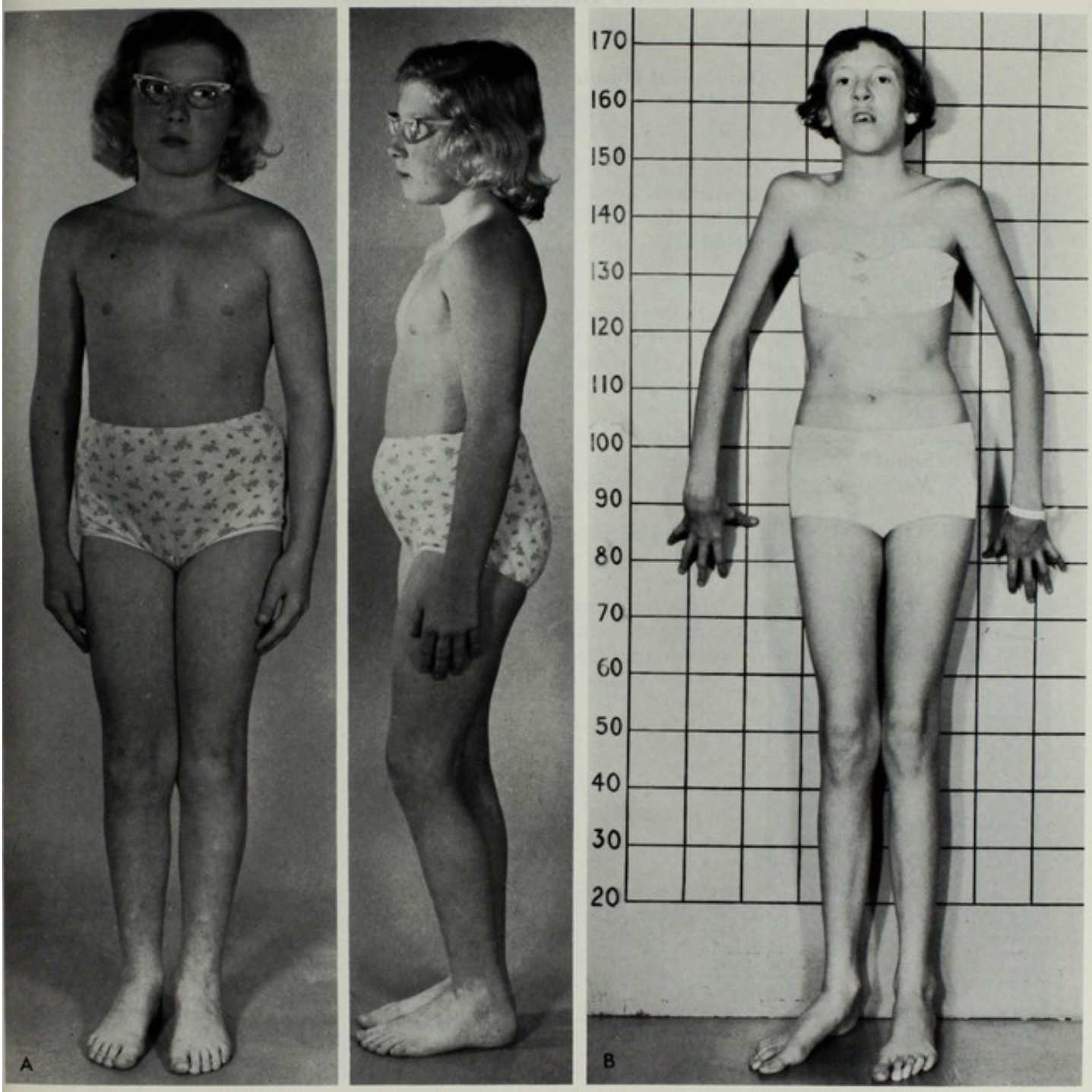
Because the degree of mental defect and the age and severity of complications vary considerably, it is not possible to state the prognosis with assurance for an affected individual.

ETIOLOGY. Autosomal recessive. Decreased cystathionine synthetase activity has been found in the liver of the parents of homocystinuric individuals, supporting the contention that they are heterozygotes.

COMMENT. The urinary cyanide nitroprusside test may not always yield a positive result in patients with homocystinuria, and specific amino acid studies therefore constitute the most important diagnostic measure. A completely successful mode of therapy has not yet been demonstrated. A low methionine, high cystine diet is being tried; unfortunately cystathionine is too expensive to warrant dietary replacement.

REFERENCES

1. Carson, N. A. J., Cusworth, D. C., Dent, C. E., Field, C. M. B., Neill, D. W., and Westall, R. G.: Homocystinuria: a new inborn error of metabolism associated with mental deficiency. Arch. Dis. Child., *38*:425, 1963.
2. Gerritsen, T., and Waisman, H. A.: Homocystinuria, an error in the metabolism of methionine. Pediatrics, *33*:413, 1964.
3. Finkelstein, J. D., Mudd, S. H., Irreverre, F., and Laster, L.: Homocystinuria due to cystathionine synthetase deficiency: the mode of inheritance. Science, *146*:785, 1964.
4. White, H. H., Thompson, H. L., Rowland, L. P., Cowen, D., and Araki, S.: Homocystinuria. Trans. Am. Neurol. Assoc., *89*:24, 1964.
5. McKusick, V.: Heritable Disorders of Connective Tissue, 4th ed. St. Louis, C. V. Mosby Co., 1972, p. 224.



A, Ten year old girl with homocystinuria who presented with lens subluxation which was first noted at four years of age. Her early developmental progress was within normal limits, but she has been receiving special schooling and her intelligence quotient is 67.

B, Twelve year old girl with arachnodactyly, "tight" joints, and inferiorly and nasally dislocated lenses. She is of low normal intelligence with a "schizoid personality" and has had two episodes of gastrointestinal bleeding, one documented as being secondary to a gastric infarct. (Courtesy of Drs. Victor McKusick and Judith Hall, Johns Hopkins Hospital.)

CAMURATI-ENGELMANN SYNDROME

(Progressive Diaphyseal Dysplasia)

Diaphyseal Dysplasia, Weakness, Leg Pain

Originally described by Cockayne in 1920, this disorder was further delineated by Camurati and then Engelmann in the 1920's. About 70 cases have been reported.

ABNORMALITIES

Skeletal. Progressive diaphyseal broadening with thickened cortices and an abrupt transition toward more normal metaphyseal bone, most evident in femur and tibia. May have sclerosis in base of skull.

Muscle. Relative weakness. Muscle biopsy may show atrophic fibers with degeneration.

Function. Waddling gait, leg pains, weakness.

OCCASIONAL ABNORMALITIES. Deafness, headaches, scoliosis, late adolescence.

NATURAL HISTORY. Severe cases may have feeding problems, waddling gait, and leg pains even in infancy and often have an asthenic "malnourished" appearance. Mild cases may only be evident by roentgenograms.

ETIOLOGY. Autosomal dominant with *wide* variance in expression.

REFERENCES

1. Cockayne, E. A.: Case for diagnosis. Proc. R. Soc. Med., *13*:132, 1920.
2. Camurati, M.: Di un raro caso di osteite simmetrica erediatria degli arti inferiori. Chir. Organi Mov., *6*:662, 1922.
3. Clawson, D. K., and Loop, J. W.: Progressive diaphyseal dysplasia (Engelmann's disease). J. Bone Joint Surg. [Am.], *46*:143, 1964.
4. Sparkes, R. S., and Graham, C. B.: Camurati-Engelmann disease. Genetics and clinical manifestations with a review of the literature. J. Med. Genet., *9*:73, 1972.



Ten and 18 year old patients showing slim habitus with bowing and angulation at the knees and flat feet. Roentgenogram shows irregular cortical thickening with diaphyseal broadening. (From Clawson, D. K., and Loop, J. W.: J. Bone Joint Surg. [Am.], *46*:143, 1964.)

EHLERS-DANLOS SYNDROME

Hyperextensibility of Joints, Hyperextensibility of Skin, Poor Wound Healing with Thin Scar

Originally described by Van Meekeren[1] in 1682, this condition was further clarified by Ehlers[2] in 1901 and Danlos[3] in 1908. More than 100 cases have been described, the most complete review being that of McKusick.[4] The possibility has been raised that the celebrated violinist Paganini may have had Ehlers-Danlos syndrome, thus accounting for his unusual dexterity and reach.

ABNORMALITIES. Most consistent features:

Face. Narrow maxilla.

Auricles. Hypermobile with tendency toward "lop ears."

Skin. Velvety, hyperextensible, and fragile with poor wound healing leaving parchment-thin scars. Small movable subcutaneous spherules contain either mucinous material or adipose.

Joints. Hyperextensibility with liability toward dislocation at hip, shoulder, elbow, knee, or clavicle. Pes planus.

Blood Vessels. Easy bruisability.

OCCASIONAL ABNORMALITIES

Eyes and Facies. Wide nasal bridge. Epicanthic folds, blue sclerae, myopia, microcornea, keratoconus, glaucoma, ectopia lentis, retinal detachment.

Skeletal. Small stature, kyphoscoliosis (27 per cent), long neck, slim skeletal build, downsloping ribs, club foot, overlapping toes. Talipes equinovarus club foot.

Dentition. Small, irregular placement, partial anodontia.

Blood Vessels. Dissecting aneurysm, intracranial aneurysm, hemorrhage.

Gastrointestinal. Inguinal hernia, diaphragmatic hernia, ectasia of intestine and intestinal diverticuli.

Renal. Ureteropelvic anomaly, renal tubular acidosis.

Other. Mental deficiency. Anomalies of mitral valve.

NATURAL HISTORY. Barabas[5] discovered that most patients with Ehlers-Danlos syndrome are born prematurely following premature rupture of the membranes, possibly the first obvious indication of relative friability of tissues in these individuals. The integrity of tissues is easily disturbed as evidenced by the fragility of skin and blood vessels. Wound healing is delayed with relatively inadequate scar tissue, and prolonged hemorrhage may occur following trauma. Both these factors plus the tendency of sutures to tear out mitigate against unnecessary surgical procedures. These patients should be cautioned to avoid traumatic situations. Gastrointestinal hemorrhage or hemoptysis may be a problem, the poor integrity of vessels may occasionally lead to a dissecting aneurysm, and affected women are liable to postpartum hemorrhage. Whether or not the tendency to chilblains and acrocyanosis is secondary to vascular alterations is undetermined.

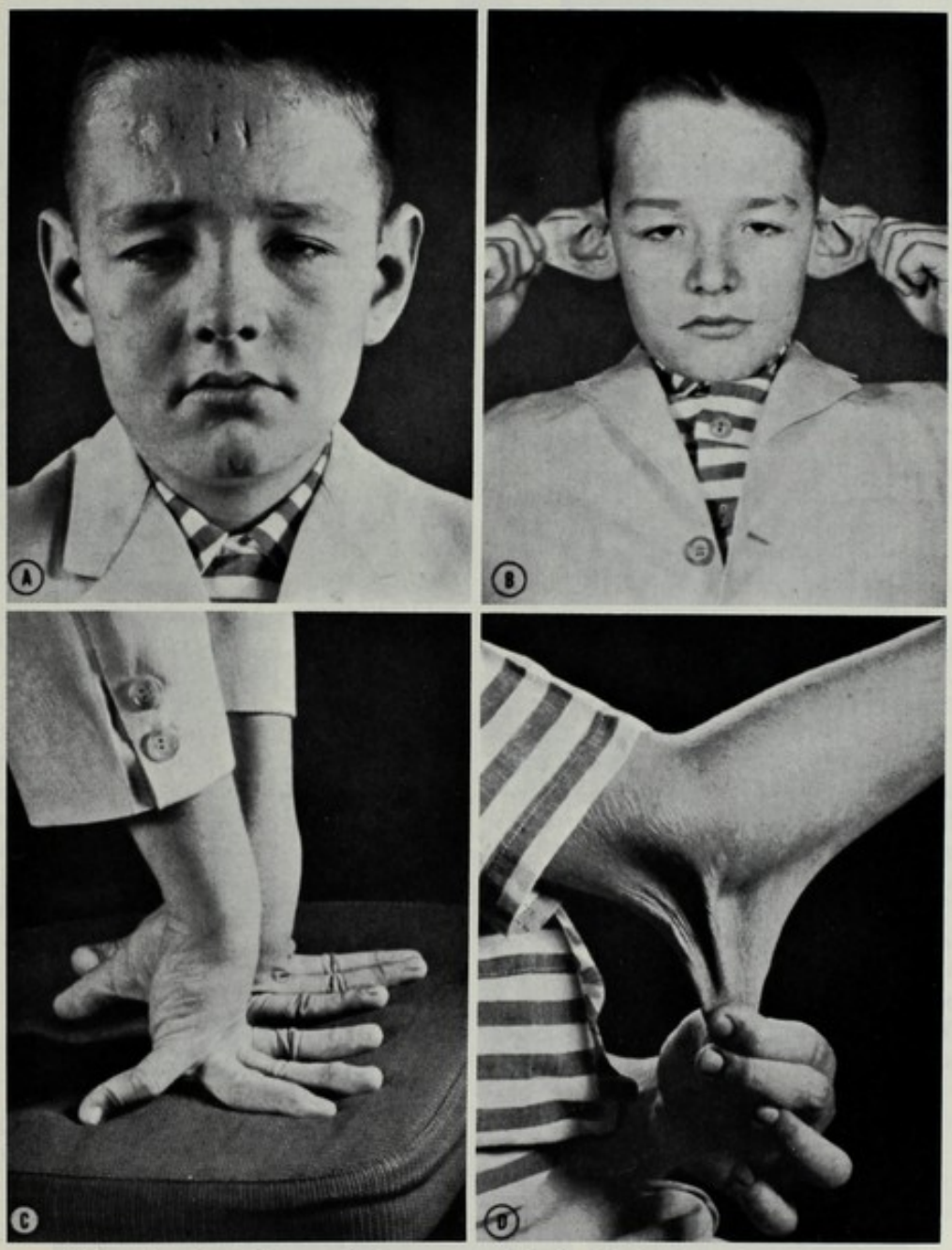
The peculiar fat- or mucinoid-containing subcutaneous spherules, most commonly found in areas of frequent mild trauma, may mineralize and thereby be evident on roentgenograms.

ETIOLOGY. Autosomal dominant with wide variance in expression. There are at least six other disorders in which loose and/or hyperextensible skin may be one feature; hence the specific diagnosis is dependent on the *total* pattern of malformation.

COMMENT. The basic problem is presumably a defect in connective tissue, most likely a defect in collagen cross-linking.

REFERENCES

1. Van Meekeren, J. A.: De dilatabilitate extraordinaria cutis. Chapter 32 in Observations Medico-chirogicae. Amsterdam, 1682.
2. Ehlers, E.: Cutis laxa, Neigung zu Harmorrhagien in der Haut, Lockerung mehrer Artikulationen. Dermat. Ztschr., *8*:173, 1901.
3. Danlos, H.: Un cas de cutis laxa avec tumeurs par contusion chronique des coudes et des genoux (santhome juvenile pseudodiabetique de MM. Hallopeau et Mace de Lepinay). Bull. Soc. Fr., Dermat. Syph., *19*:70, 1908.
4. McKusick, V. A.: Heritable Disorders of Connective Tissue, 3rd ed. St. Louis, C. V. Mosby Co., 1966, p. 179.
5. Barabas, A. P.: Ehlers-Danlos syndrome: associated with prematurity and premature rupture of foetal membranes; possible increase in incidence. Br. Med. J., *2*:682, 1966.
6. Wechsler, H. L., and Fisher, E. R.: Ehlers-Danlos syndrome. Pathologic, histochemical, and electron microscopic observations. Arch. Pathol., *77*:613, 1964.



Twelve year old boy showing thin persisting scars on forehead *(A)*, hyperelasticity of auricles and skin *(B and D)*, and hyperextensibility of joints *(C)*. (From Rees, T. D., et al.: Plast. Reconstr. Surg., *32*:39, 1963)

OSTEOGENESIS IMPERFECTA TARDA SYNDROME

(Autosomal Dominant Osteogenesis Imperfecta, Lobstein Disease)

Fragile Bone, Blue Sclerae, Hyperextensibility, and/or Odontogenesis Imperfecta

This rather generalized disorder of connective tissue occurs with a frequency of about one in 25,000 individuals. There is wide individual variability in the manifestations of the disease, and the following individual defects occur in roughly 25 to 60 per cent of patients, with no alteration being a consistent feature.

ABNORMALITIES

Growth. Small stature in severe cases, sometimes with unduly short limbs.

Bones. Thin cortices and sparse trabeculae with fragility leading to bowing of leg bones in severe cases. Occasionally soft thin calvarium with wide fontanels and wormian bones, with bulging in temporal and frontal regions and platybasia at base of skull; biconcave flattening of vertebrae; pectus carinatum or excavatum. Small facial bones.

Joints and Ligaments. Hyperextensible, sometimes leading to kyphoscoliosis, flat feet, and in extreme cases joint dislocation.

Dentition. Hypoplasia of dentin and pulp with translucency of teeth which have a yellowish or bluish-gray coloration, and propensity to caries, irregular placement, and late eruption.

Sclerae and Skin. The skin and sclerae tend to be thin and translucent, with partial visualization of the choroid, giving the sclerae a blue appearance.

Hearing. Deafness is usually secondary to otosclerosis and is seldom present until adult life.

Other. Inguinal and/or umbilical hernia. Poor muscle development. Increased bleeding tendency secondary to capillary fragility and/or abnormal thrombocyte function.

OCCASIONAL ABNORMALITIES

Eye. Embryotoxon (opacity in the peripheral cornea), keratoconus, megalocornea.

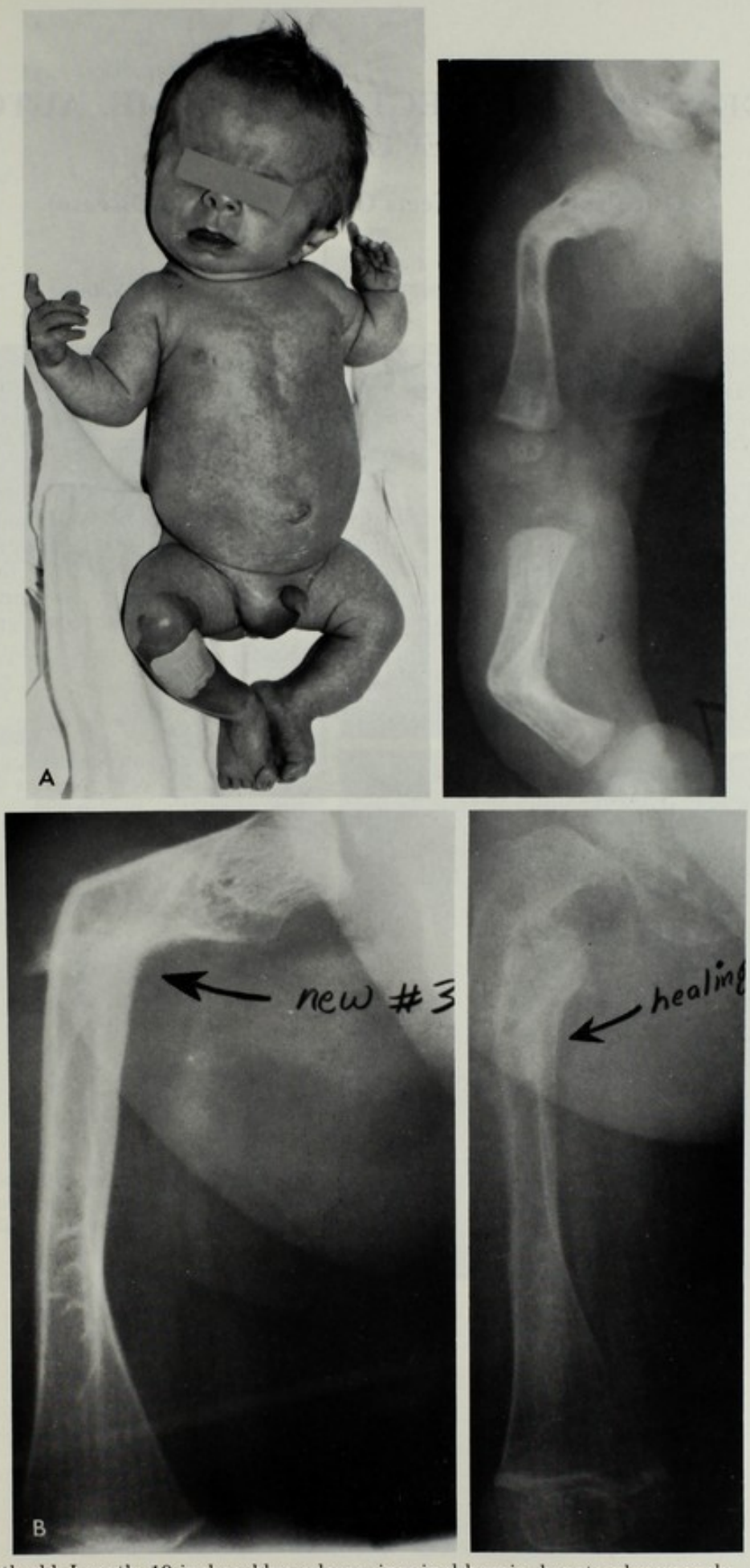
Other. Syndactyly. Floppy mitral valve.

NATURAL HISTORY. There is wide individual variability with early mortality among severely affected infants, chiefly related to bronchopneumonia. Beyond infancy the outlook for survival is good, and the chief problems are orthopedic deformity and otosclerosis. The long leg bones are the most frequent site of breakage with the peak ages for fractures being two to three years and ten to 15 years. After adolescence the likelihood of fracture diminishes, although inactivity, pregnancy, or lactation can apparently enhance the likelihood of fracture. Intramedullary support by metal rods should be considered for treatment of the serious multiple fracture cases, and optimal orthopedic management is merited because many of these patients make a surprisingly good life adaptation. By 30 to 39 years of age, 35 per cent of patients have deafness; it occurs in 50 per cent by 60 years of age.

ETIOLOGY. Autosomal dominant. The majority of severe cases represent a sporadic occurrence within the family, presumably a fresh gene mutation, for which the parents need have little concern for recurrence. However, these sporadic cases should be distinguished from the autosomal recessive severe type of osteogenesis imperfecta. Cropp and Myers[5] have reported evidence of hypermetabolism in patients with this disorder. Though the basic etiology is undetermined, their findings are of interest.

REFERENCES

1. McKusick, V. A.: Heritable Disorders of Connective Tissue, 3rd ed. St. Louis, C. V. Mosby Co., 1966.
2. Herndon, C. N.: Osteogenesis imperfecta: some clinical and genetic considerations. Clin. Orthop., *8*:132, 1956.
3. Freda, V. J., Vosburgh, G. J., and Di Liberti, C.: Osteogenesis imperfecta congenita. A presentation of 16 cases and review of the literature. Obstet. Gynecol., *18*:535, 1961.
4. Smars, G.: Osteogenesis Imperfecta in Sweden. Clinical, Genetic, Epidemiological, and Socio-Medical Aspects. Stockholm, Scandinavian University Books, 1961.
5. Cropp, G. J. A., and Myers, D. N.: Physiologic evidence of hypermetabolism in osteogenesis imperfecta. Pediatrics, *49*:375, 1972.



A, Two month old. Length, 19 inches; blue sclerae, inguinal hernia, hepatosplenomegaly.

B, Seventeen month old with a third fracture which was healing well by 18 months. Note the thin cortices and the ground glass "washed-out" appearance of the bone.

OSTEOGENESIS IMPERFECTA SYNDROME, AUTOSOMAL RECESSIVE

(Osteogenesis Imperfecta Congenita, Vrolik Disease)

Short Broad Long Bones, Multiple Fractures, Blue Sclerae

The occurrence of a severe congenital broad-boned type of osteogenesis imperfecta in siblings of normal parents now seems well established.[1, 2]

ABNORMALITIES

Growth. Prenatal short-limbed growth deficiency.

Craniofacial. Poorly mineralized soft calvarium with large fontanels and multiple Wormian bones. Deep blue sclerae, shallow orbits, small nose, low nasal bridge.

Limbs. Short thick "ribbon-like" poorly mineralized long bones with multiple fractures and callus formation, especially in lower limbs.

Other. Flattened vertebrae, hypotonia, inguinal herniae, variable hydrocephalus.

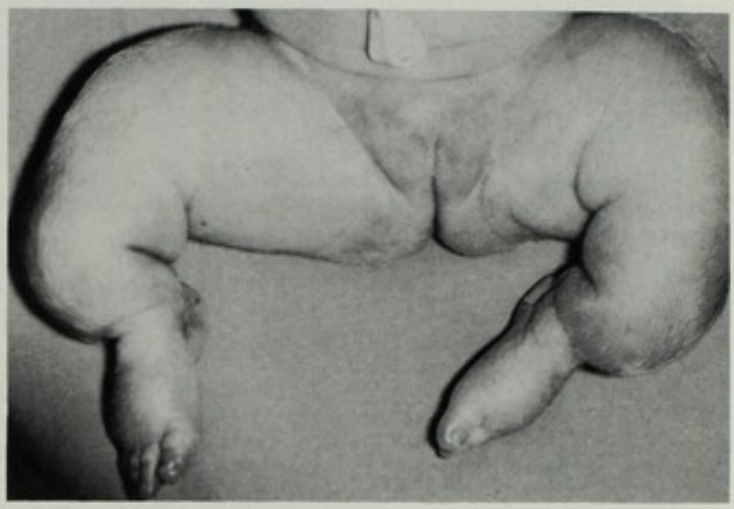
NATURAL HISTORY. These patients are usually stillborn or die in early infancy. If they survive, progressive hydrocephalus may develop and cystic changes may take place in the long bones of the lower limbs.

ETIOLOGY. Autosomal recessive. An occasional patient with the autosomal dominant type of osteogenesis imperfecta may be severely affected at birth. Therefore, the family should be closely evaluated before assuming that the patient has the autosomal recessive type.

REFERENCES

1. McKusick, V. A.: Osteogenesis imperfecta. *In* Heritable Disorders of Connective Tissue. St. Louis, C. V. Mosby Co., 1972, p. 390.
2. Remigo, P. A., and Grinvalsky, H. T.: Osteogenesis imperfecta congenita. Am. J. Dis. Child., *119*:524, 1970.







Young infant of normal parents. (Courtesy of P. Baird, University of British Columbia Department of Medical Genetics.)

FIBRODYSPLASIA OSSIFICANS CONGENITA SYNDROME

Short Hallux, Fibrous Dysplasia Leading to Ossification in Muscles and Subcutaneous Tissues

This condition, described in a letter by Guy Patin in 1692, was extensively reviewed by Rosenstirn in 1918.[1] Fibroplasia ossificans congenita is the terminology utilized by McKusick[2] because myositis ossificans congenita is basically a misnomer. More than 350 cases have been reported.

ABNORMALITIES[1-3]

Digits. Short hallux, often with synostosis. Less frequently, short thumb.

Fibrous Tissues. Swellings, sometimes with pain and fever, in aponeuroses, fasciae, and tendons leading to ossification in muscles and fibrous tissues; most prominent in neck, dorsal trunk and proximal limbs with sternocleidomastoid frequently involved.

OCCASIONAL ABNORMALITIES. Short phalanges other than hallux or thumb, clinodactyly of fifth finger, short femoral neck, hernia. Widely spaced teeth. Hypogenitalism and/or delayed sexual development.

NATURAL HISTORY. The unusual fibrodysplasia leading to ossification may have become evident during fetal life or as late as 25 years, most patients experiencing onset in early childhood. Ossification is usually evident within two to eight months of the time swelling occurred. Although some affected individuals never express the fibrodysplasia and others survive to late adult life with severe disability, the majority who have fibrodysplasia within the first five years succumb to the consequences of severe immobilization prior to 15 years of age. No effective treatment has been discovered, although symptomatic relief of pain may be achieved by salicylates or hydrocortisone analogue therapy. The natural history tends toward exacerbation and remission, and therefore the results of therapy should be interpreted with caution. Another matter for caution is the interpretation of biopsies from affected tissues. The pathologic interpretation may be osteogenic sarcoma, although such a malignant growth is not a feature of this disease.

ETIOLOGY.[3] Autosomal dominant with almost full penetrance for short hallux and varying expression for the fibrodysplasia. About 90 per cent of cases represent fresh mutations for which older paternal age has been noted as a factor.

COMMENT. Although the fundamental defect in fibrous tissue is unknown, it is obvious that it allows for ossification to normal appearing bone in tissues in which ossification would normally not occur.

REFERENCES

1. Rosenstirn, J.: A contribution to the study of myositis ossificans progressiva. Ann. Surg., *68*:485, 1918.
2. McKusick, V.: Heritable Disorders of Connective Tissue, 3rd ed. St. Louis, C. V. Mosby Co., 1966, p. 400.
3. Tünte, W., Becker, P. E., and v. Knorr, G.: Zur Genetik der Myositis ossificans progressiva. Humangenetik, *4*:320, 1967.









Seven-year-old with secondary torticollis, scoliosis, and partial contractures at elbow, hip, and knee joints. Note the short and deformed first metatarsal, hallux, and first metacarpal. Aberrant ossification is evident in the lower thigh. (From Herrmann, J., et al.: Birth Defects. Original Article Series, Vol. V, No. 5, May 1969. Courtesy of Dr. John M. Opitz, University of Wisconsin.)

PSEUDOXANTHOMA ELASTICUM SYNDROME

Thickened Yellowish Flexural Skin, Angioid Retinal Streaks, Medial Arterial Degeneration with Hemorrhagic Tendency

This disease, so aptly described by McKusick,[1] appears to be the consequence of degeneration in the collagenous-elastic tissue with accumulation of elastic-appearing fibers, many in fragmented form.

ABNORMALITIES

Skin. Thick, grooved, lax yellowish skin in flexures and other areas of wear, often involving oral mucous membranes.

Eye. Retinal breaks with angioid streaks and degeneration. Impaired vision, about 20 years after skin lesions develop.

Cardiovascular. Arterial medial thickening with secondary vascular insufficiency leading to diminished or absent pulses, intermittent claudication, and angina pectoris.

Vascular hemorrhagic tendency with bleeding into gastrointestinal tract and many other sites.

Thickening of endocardium including valve leaflets.

Calcification. Within degenerating tissues, i.e., subcutaneous, vascular, and falx cerebri.

NATURAL HISTORY. Skin changes, though they may be present from early in life, are usually not recognized until the second decade or later. Visual impairment is frequent, and hemorrhagic episodes can be severe. The frequent psychic and neurologic problems are possibly secondary to central nervous system hemorrhages, vascular insufficiency, or both.

ETIOLOGY. Autosomal recessive.

REFERENCES

1. McKusick, V. A.: Heritable Disorders of Connective Tissue. 4th ed. St. Louis, C. V. Mosby Co., 1972.
2. Alinder, I., and Bostrom, H.: Clinical studies on a Swedish material of pseudoxanthoma elasticum. Acta Med. Scand., *191*:273, 1972.



Posterior-oblique view of neck of an adolescent female showing thickened and grooved skin which had a yellowish-pink coloration.

HAMARTOSES

Disorders in Which Hamartomata Are a Prominent Feature

Hamartosis implies an organizational defect leading to an abnormal admixture of tissues, often with a tumor-like excess of one or more components of the tissue. Included in this category are such features as hemangiomata, melanomata, irregular skin pigmentation, fibromata, lipomata, osteomata, dental tumors, and adenomata. There are also some strange tissue admixtures which create nosologic confusion because the histology of the lesions does not conform to a pathologic standard. For example the "adenoma sebaceum" lesions in tuberous sclerosis are not adenoma of sebaceous glands. The very name tuberous sclerosis – potato-like lesions with sclerosis in the brain – emphasizes the nosologic problems.

The aberrant growth of particular tissues, a feature of many hamartomata, may allow for local growth toward a tumor, or even metastasis beyond the local site. One advantage in recognizing some of the following patterns of malformation is the enhanced capability of anticipating future problems by knowing the natural history of the disorder. For example, malignant change of a colonic polyp in the Gardner syndrome is sufficiently frequent to justify resection of the colon by the age of 12 in a child who is recognized as having this syndrome with colonic polyps. However, in another syndrome with intestinal polyposis – the Peutz-Jeghers syndrome – the natural history indicates that intestinal malignancy is a rare occurrence, an important fact because the intestinal polyps excised from patients with the Peutz-Jeghers syndrome may be interpreted by the pathologist as potentially malignant.

The "occasional abnormalities" in some of the following syndromes may be "occasional tumors." The physician should be on guard for the occasional rhabdomyoma in tuberous sclerosis, the ovarian tumor in the Gardner syndrome, and the medulloblastoma in the basal cell nevus syndrome.

Hamartomatous lesions are a feature of many syndromes other than those which follow. For example, multiple exostoses represent a hamartomatous process in the diaphyseal portion of the bone, and this condition carries a small but distinct risk toward the development of osteosarcoma. Melanomata are a frequent feature in the XO (Turner) syndrome. Adrenal carcinoma and Wilms' tumor are occasional complications for individuals with the Beckwith- Wiedemann syndrome. A looser association, in terms of being a distinct syndrome, has been noted in the occurrence of Wilms' tumor in individuals with hemihypertrophy, aniridia, or both. These types of cases emphasize the close relationship which may exist between malformation and neoplasia. The same mutant gene which gives rise to an altered facies in the basal cell nevus syndrome also affects the growth stability of certain cells, allowing for nevi as a usual feature and basal cell carcinoma from such lesions as an occasional feature.

Finally, there would appear to be little value in persisting with the use of the term "phacomatoses" for some of the following conditions. The original "phacomatoses" – Sturge-Weber anomalad, tuberous sclerosis, and neurofibromatosis – may now be viewed as separable entities, clinically distinct from each other, with no apparent etiologic relationship.

STURGE-WEBER ANOMALAD

Flat Facial Hemangiomata, Meningeal Hemangiomata with Seizures

The association and localization of aberrant vasculature in the facial skin, eye, and meninges is compatible with there having been a single early localized defect in vascular morphogenesis at a very early stage of development in the tissue from which the vasculature of these three regions eventually develops, prior to the development of the iris and before the craniofacial skeleton has formed.

ABNORMALITIES[1, 2]

Facial. Pink to purplish-red nonelevated cutaneous hemangiomata, most commonly in a trigeminal facial distribution, sometimes involving the choroid of the eye with secondary buphthalmos, glaucoma.

Meninges and Central Nervous System. Hemangiomata of arachnoid and pia, especially in occipital and temporal areas with secondary cerebral cortical atrophy, sclerosis, and "double-contour" convolutional calcification. Seizures, paresis, mental deficiency.

OCCASIONAL ABNORMALITIES. Hemangiomatosis in nonfacial areas, central nervous system, other tissues. Macrocephaly. Cavernous hemangiomata. Colobomata of iris, coarctation, abnormal external ears.

NATURAL HISTORY. The surface cutaneous hemangiomata are usually present at birth and seldom progress. Seizures most commonly begin between two months and seven months of age and are grand mal in type, often asymmetrical. The degree of central nervous system involvement is variable, with 30 per cent having paresis and 56 per cent having seizures; not all patients are mentally deficient. Cerebral calcification is usually not evident by X-ray until latter infancy, the earliest being in a patient 13 months of age, being first noted in the occipital region.

Medical anticonvulsant treatment is of limited value, and occasionally partial extirpation of affected meninges, brain tissue, or both may be merited in unilateral cases as a measure to control the seizures.

ETIOLOGY. Unknown. Sporadic, with rare exceptions. Occasionally other family members may have hemangiomata of a lesser degree.

REFERENCES

1. Chao, D. H.-C.: Congenital neurocutaneous syndromes of childhood. III. Sturge-Weber disease. J. Pediatr., *55*:635, 1959.
2. Butterworth, T., and Strean, L. P.: Clinical Genodermatology. Baltimore, The Williams and Wilkins Co., 1962.





A, Affected child who has had grand mal seizures.
B, Note the fine mineralization (left), which tends to reflect the convolutional pattern of the brain.

NEUROCUTANEOUS MELANOSIS ANOMALAD

Melanosis of Skin and Pia-Arachnoid, CNS Deterioration

This melanocytic hamartomatosis of skin and pia-arachnoid was described in 1861. More than 21 cases have been reported,[3]

ABNORMALITIES[3]

Skin. Blackish, thickened, sometimes hairy multiple nevi, most extensive in a "bathing trunk" distribution over the lower trunk, abdomen, and upper thigh.

Pia-Arachnoid. Thick and pigmented with nests and sheets of melanoblasts, most striking at base of brain.

CNS. Liable to development of seizures and deterioration of central nervous system function.

NATURAL HISTORY. The cutaneous melanosis is grossly evident at birth. Central nervous system function may initially be normal, but seizures and mental deterioration may begin before one year of age, apparently related to progression of the melanoblastic involvement of the pia-arachnoid, with diffuse or localized malignancy being implied in 12 of 18 cases. Macroscopic pigmentation was evident in the cerebellum in 7 cases and cerebral cortex in 1 of the necropsy cases. Hydrocephalus of prenatal onset was reported in 1 case.[3]

The CNS consequences of the disorder often result in early demise. Three of the recognized cases were stillborn; the majority died before 2 years of age, and only one sixth of the cases are known to have survived past the age of 25 years.[3]

ETIOLOGY. Sporadic, cause unknown. Presumed to be an aberration in growth of early melanoblasts of neural crest origin which contribute to skin and pia-arachnoid. The sex incidence has been equal and a family history of melanomata was noted in only one case.[2]

REFERENCES

1. Rokitansky, J.: Ein ausgezeichneter Fall von Pigment-mal mit ausgebreiteter Pigmentirung der inneren Hirn- und Rückenmarkshäute. Allg. Wien Med. Ztg., *6*:113, 1861.
2. Van Bogaert, L.: La mélanose neurocutanée diffuse hérédofamiale. Bull. Acad. R. Med. Belg. (6th Series), *13*:397, 1948.
3. Fox, H., Emery, J. L., Goodbody, R. A., and Yates, P. O.: Neurocutaneous melanosis. Arch. Dis. Child., *39*:508, 1964.



Infant who as yet shows no signs of CNS involvement. (Courtesy of S. Bintliff, Kauikeolani Children's Hospital, Honolulu.)

LINEAR SEBACEOUS NEVUS ANOMALAD

(Nevus Sebaceus of Jadassohn)

Midfacial Nevus Sebaceus, Seizures, Mental Deficiency

Nevus sebaceus of Jadassohn is most commonly found in an otherwise normal individual.[1] However, the association of this type of lesion in the midfacial area in conjunction with seizures and mental deficiency has been reported in at least 11 cases.[2-5]

ABNORMALITIES[2-4]

Skin. Nevus sebaceus with hyperpigmentation and hyperkeratosis. Lesions most commonly in the midfacial area, from the forehead down into the nasal area, tending to be linear in distribution. May also affect trunk and limbs.

CNS. Seizures of major motor, focal, or minor motor type. Mental deficiency.

OCCASIONAL ABNORMALITIES

Eye. Esotropia, lipodermoid of conjunctiva, cloudy cornea, colobomata of eyelid, coloboma of iris and choroid.

CNS. Asymmetric "cortical atrophy," hydrocephalus.

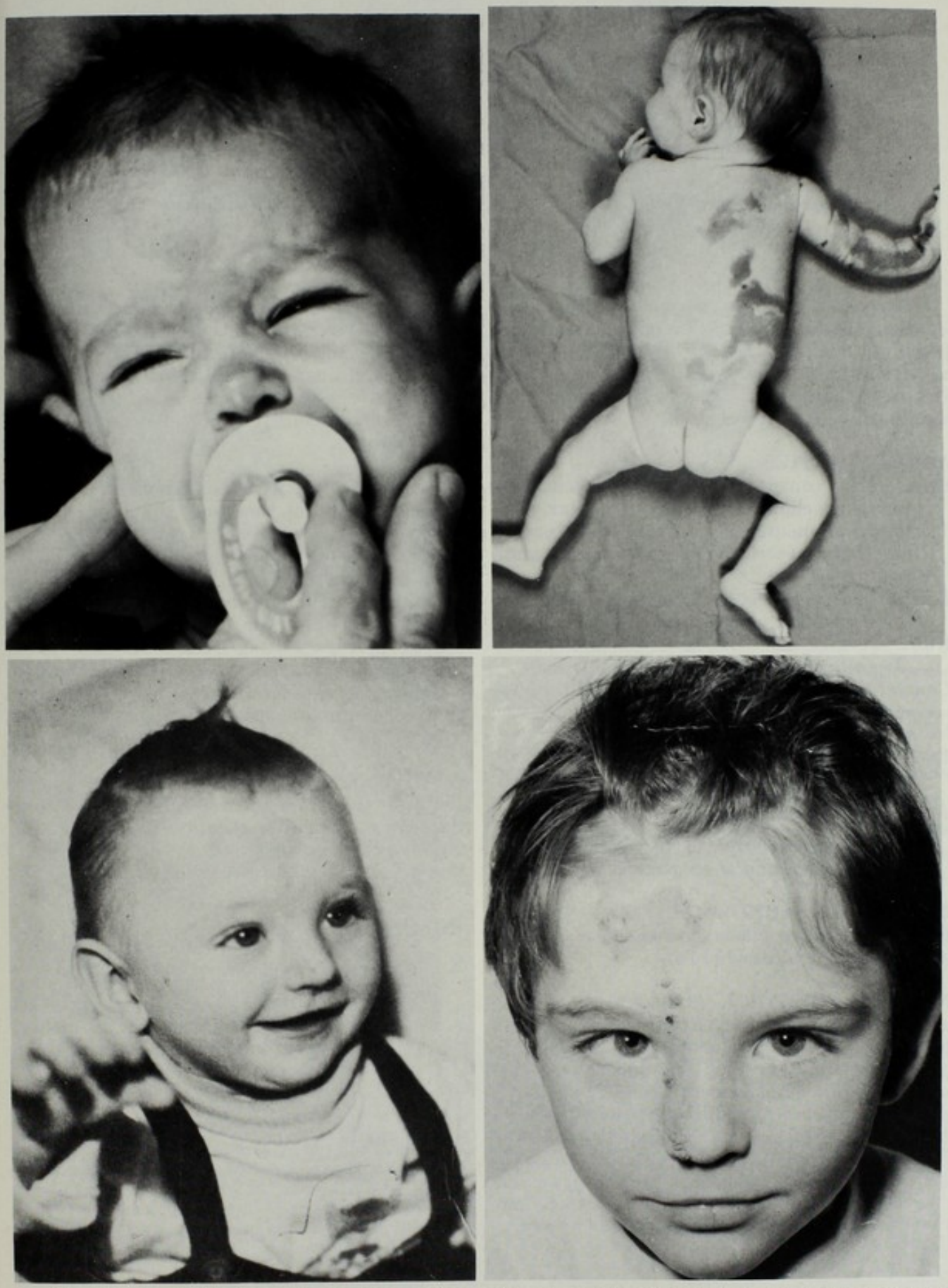
Other. Pigmented nevi, spotty alopecia, coarctation of aorta, ventricular septal defect, hypoplastic teeth. Renal hamartomas, nephroblastoma.

NATURAL HISTORY. The nevus sebaceus is usually present at birth as a slightly yellow to orange to tan waxy-appearing lesion containing deficiencies and/or papillomatous excesses of epidermal elements, especially sebaceous glands and immature hair follicles. With time the lesions tend to become verrucous and unsightly. Surgical removal should be considered, since there is a 15 to 20 per cent risk of tumor, especially basal cell epithelioma. In the cases with associated central nervous system features, the onset of seizures has been from two months to two years and they are difficult to control. The mental deficiency has been moderate to severe, though an occasional patient may have normal intelligence.

ETIOLOGY. Unknown. Whether this constitutes a single etiologic entity remains to be determined. Bianchine[4] noted seizures and/or mental deficiency without skin lesions in several first-degree relatives of one patient. Hence, a cautious family evaluation is merited in cases of this clinical disorder.

REFERENCES

1. Mehregan, A. H., and Pinkus, H.: Life history of organoid nevi. Special reference to Nevus Sebaceus of Jadassohn. Arch. Dermatol., *91*:574, 1965.
2. Feurerstein, R. C., and Mims, L. C.: Linear nevus sebaceus with convulsions and mental retardation. Am. J. Dis. Child., *104*:675, 1962.
3. Marden, P. M., and Venters, H. D.: A new neurocutaneous syndrome. Am. J. Dis. Child., *112*:79, 1966.
4. Bianchine, J. W.: The nevus sebaceous of Jadassohn. A neurocutaneous syndrome and a potentially premalignant lesion. Am. J. Dis. Child., *120*:223, 1970.
5. Lansky, L. L., et al.: Linear sebaceous nevus syndrome. Am. J. Dis. Child., *123*:587, 1972.



Above, Two week old with facial and extensive body sebaceous nevi. Intractable seizures began at five months and the patient died at nine months with pneumonia. Necropsy revealed renal nodular nephronoblastomatosis. (From Lansky, L. L., et al.: Am. J. Dis. Child., *123*:587, 1972.)

Below, Verrucous change in sebaceous nevus from infancy to older childhood. (From Bianchine, J. W.: Am. J. Dis. Child., *120*:223, 1970.)

INCONTINENTIA PIGMENTI SYNDROME

(Bloch-Sulzberger Syndrome)

Irregular Pigmented Skin Lesions with or without Dental Anomaly, Patchy Alopecia

Bardach[1] originally described the condition in twin sisters in 1925, and soon thereafter Bloch[2] set forth the term incontinentia pigmenti to depict the unusual skin lesions. More than 200 cases have been described, of which less than 5 per cent have been males.

ABNORMALITIES

Skin. Most consistent feature. Vesiculation, verrucous changes, atrophy, irregular gray-brown pigmentation in fleck, whorl or spidery form, especially on trunk and extremities.

Teeth. Thirty per cent have hypodontia, delayed eruption, and/or conical form.

Hair. Twenty per cent have atrophic patchy alopecia, especially on the posterior scalp.

Central Nervous System. About one third have mental deficiency, microcephaly, spasticity, and/or seizures.

Eye. About 30 per cent have strabismus, retinal dysplasia, uveitis, keratitis, cataract, retrolental dysplasia, and/or blue sclerae.

Osseous. About 20 per cent have hemivertebrae, kyphoscoliosis, extra rib, syndactyly, hemiatrophy, and/or short arms and legs.

OCCASIONAL ABNORMALITIES. Nail dystrophy, breast hypoplasia, dacrostenosis, eczema, short stature, hydrocephalus.

NATURAL HISTORY. Bullous skin lesions are generally present in early infancy and tend to progress from inflammatory or vesicular to pigmented and may fade in childhood. General eosinophilia is often present in infancy and the vesicles contain eosinophils. Verrucous lichnoid lesions develop during infancy in about one third of cases, especially over the dorsum of the hands and feet. The development of the irregular "marble-cake-like" pigmentation may or may not coincide with the sites of bullous or verrucous lesions. The pigmented areas gradually fade in the second to third decades and the adult may only show slightly atrophic depigmented "achromic stains," especially over the lower legs. About half the patients show other features, the most serious being the central nervous system abnormalities.

ETIOLOGY. Family studies indicate the effect of a single mutant gene, most likely a lethal in affected males because the ratio of females to males in affected sibships is 2:1 with half the females affected. Whether the gene is autosomal or X-linked remains to be determined. About 15 to 40 per cent of the cases are familial, the remainder representing fresh mutational cases. The parents, especially the mother, should be closely examined for residual skin lesions, including achromatic spots, before genetic counsel is rendered.

COMMENT. Palmgren,[4] who cultured herpes simplex virus from the vesicular fluid of a patient, has raised the question of whether this viral agent may contribute to the expression of this genetically determined disease.

REFERENCES

1. Bardach, M.: Systematisierte Naevusbildungen bei einem cineiigen Zwillingspaar. Ein Beitrag zur Naevusätiologie. Z. Kinderheilkd., *39*:542, 1925.
2. Bloch, B.: Eigentümliche bisher nicht beschreibene Pigmentaffektion (Incontinentia pigmenti). Schweiz. Med. Wochenschr., *56*:404, 1926.
3. Carney, R. G.: Incontinentia pigmenti. A report of five cases and review of the literature. Arch. Dermatol. Syph., *64*:126, 1951.
4. Palmgren, B.: The relationship of dermatitis herpetiformis to incontinentia pigmenti in newborn infants. Pediatrics, *29*:295, 1962.
5. Morgan, J. D.: Incontinentia pigmenti. Am. J. Dis. Child., *122*:294, 1971.









A, Early lesions in the young infant shown in *B*.

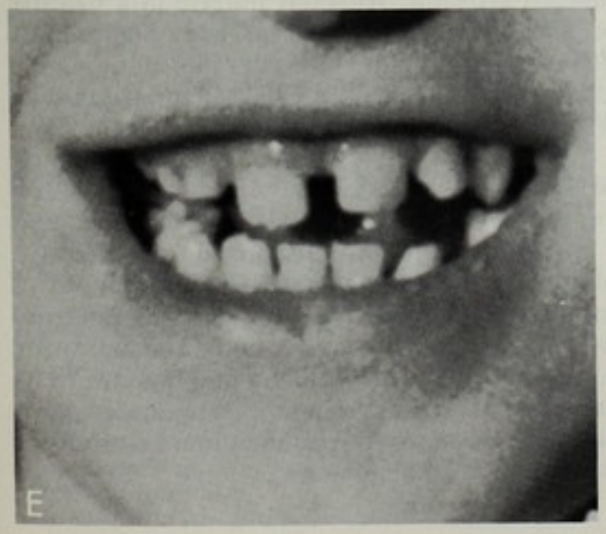
C, Older mentally deficient infant with reticular pigmentation.

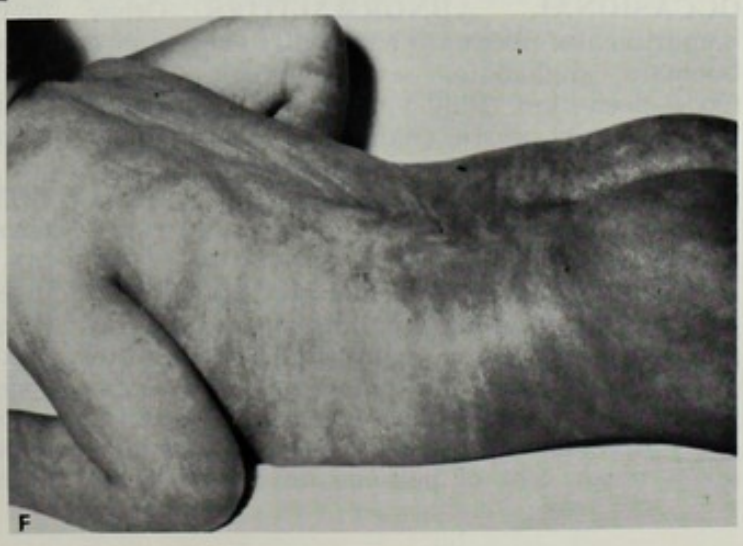
D, Mentally deficient woman with spasticity and pseudogliomatous retinal detachment, showing advanced skin pigmentary change.

E, Minor abnormalities of dentition in an affected girl.

F, Reticular pigmentation in a three year old mentally deficient girl.

(*A* to *E* courtesy of J. M. Opitz, University of Wisconsin.)





TUBEROUS SCLEROSIS SYNDROME

(Adenoma Sebaceum)

Hamartomatous Skin Nodules, Seizures, Phakomata, Bone Lesions

Von Recklinghausen is said to have described this disease over 100 years ago, but Bourneville[1] is usually given credit for its recognition in 1880. Hamartomatous lesions develop in many tissues, especially the skin and brain. About 0.5 per cent of severely mentally defective individuals have this condition.

ABNORMALITIES

Brain and Eye. Glioma-angioma lesions in cortex and white matter with seizures (93 per cent) and mental deficiency (62 per cent) as apparent consequences. Roentgenographic evidence of intracranial mineralization (51 per cent), most commonly in basal ganglia or periventricular region. Phakomata, similar retinal lesions, in 53 per cent.

Skin. Fibrous-angiomatous lesions (83 per cent), varying in color from flesh to pink to yellow to brown, develop in nasolabial fold, cheeks, and elsewhere. Ovaloid "white nevi" from 0.5 to 8 cm in size which contain melanocytes without melanin. Café-au-lait spots. Fibromatous plaques, nodules.

Bone. Cyst-like areas in phalanges (66 per cent) and elsewhere, with areas of periosteal thickening, yielding x-ray evidence of "sclerosis," palpable irregularity, or both.

Kidney. Angiomyolipomata in 45 to 81 per cent, usually multiple and benign. Tubular enlargement and cyst formation with hyperplasia of tubular cells.

OCCASIONAL ABNORMALITIES. Other hamartomata: fibromata (especially subungual), lipomata, angiomata, nevi, shagreen patches (goose-flesh-like). Rhabdomyomata and angiomata of heart, cystic changes in lung, hamartomata of liver and pancreas. Hypothyroidism, thyroid adenomata. Sexual precocity. Astrocytoma.

NATURAL HISTORY. Hamartomata usually become evident in early childhood and may increase at adolescence. Facial nodular lesions are present in 50 per cent of children by five years, whereas 82 per cent have white nevi in childhood. Malignant transformation may occur, and about 6 per cent of patients develop a brain tumor. The seizures, which tend to develop in early childhood, may initially be myoclonic and later grand mal in type and are difficult to control. EEG abnormality is found in 87 per cent of patients and may be of the grossly disorganized hypsarrhythmic pattern. The seizures and mental defect seem to be related to the extent of hamartomatous change in the brain. For those with mental deficiency 100 per cent have seizures, 88 per cent by five years of age, whereas of those without serious mental deficiency 69 per cent have seizures, 44 per cent by five years of age. Mental deterioration is unusual, except in relation to frequent seizures of status epilepticus.

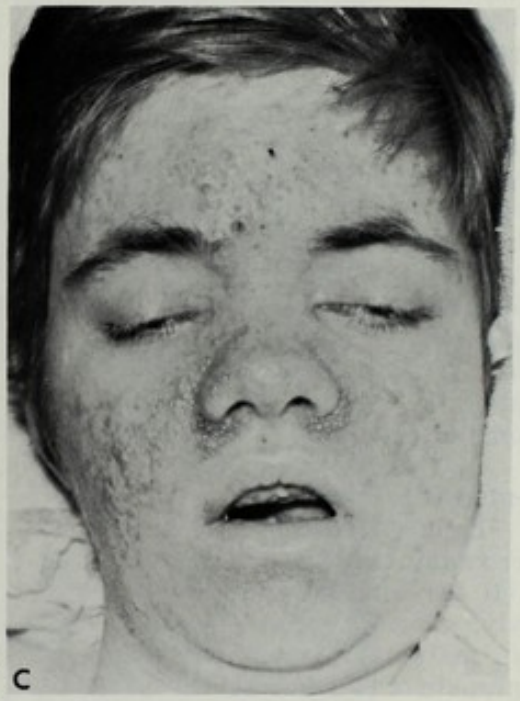
An unknown percentage of patients die prior to 20 years of age as the consequence of status epilepticus, general debility, pneumonia, or tumor. However, it should be appreciated that there is wide variability in expression of the disease; all patients with skin lesions do not develop seizures, mental deficiency, or both, and the earlier-noted pattern of abnormality is biased toward the more severe cases. One general survey showed a 69 per cent incidence of mental deficiency. However, of the nine ascertained at a hospital for skin diseases none were mentally deficient, whereas 93 per cent of those admitted to a children's hospital were mentally deficient.

ETIOLOGY. Autosomal dominant with about 86 per cent representing fresh mutations from unaffected parents. Affected individuals usually show some manifestations of the disorder by adulthood. Older paternal age has not been a factor in fresh mutational cases of tuberous sclerosis.

COMMENT. The reader will note that the term "adenoma sebaceum" is not utilized, and this is because the skin lesions do not directly involve the sebaceous glands. Actually the term tuberous sclerosis (potato-like sclerotic lesions) pertains only to the brain lesions and is a poor eponym for this disease. Such eponyms are indicative of the difficulty in applying descriptive names to these admixed hamartomatous areas of faulty tissue morphogenesis.







A, Two year old with early pink to red nodular and flat skin lesions and seizures.
B, Girl with mental deficiency and seizures.
C, Young woman with mental deficiency and seizures, on Dilantin therapy.
(*B* and *C* courtesy of L. Dobbs, Rainier State Training School, Washington.)

REFERENCES

1. Bourneville, D.: Sclereuse tubereuse des circonvolutions cerebrales. Idiote et epilepsie hemiplegique. Arch. Neurol. (Paris), *1*:81, 1880.
2. Lagos, J. C., and Gomez, M. R.: Tuberous sclerosis: reappraisal of a clinical entity. Mayo Clin. Proc., *42*:26, 1967.
3. Bundey, S., and Evans, K.: Tuberous sclerosis: A genetic study. J. Neurol. Neurosurg. Psychiatry, *32*:591, 1969.

NEUROFIBROMATOSIS SYNDROME

Multiple Neurofibromata, Café-au-Lait Spots, with or without Bone Lesions

Von Recklinghausen[1] described this disease in 1882. Crowe, et al.[2] estimated the incidence at one in 3000 individuals.

ABNORMALITIES

Skin. Areas of hyper- or hypopigmentation with café-au-lait spots in 94 per cent, roughly three fourths of affected individuals having six or more spots measuring 1.5 cm. or greater in size, most commonly on trunk. Axillary "freckling" may occur.

Subcutaneous. Dysplastic tumors consisting of connective tissue, neurolemma cells, and/or mast cells; occurring along nerves, in subcutaneous tissues, and sometimes in eye and/or meninges.

OCCASIONAL ABNORMALITIES

Skeletal. Scoliosis, hypoplastic bowing of lower leg with pseudoarthrosis at birth, osseous lesions with localized osteosclerosis, rib fusion, spina bifida, absence of patella, dislocation of radius and ulna, local overgrowth, and scalloping of vertebral bodies with deformed pedicles.

Hamartomata. Cutaneous nevi, lipomata, angiomata.

Neurofibromata in kidney, stomach, heart, tongue.

Fibrosing alveolitis of lung.

Endocrine. Acromegaly, sexual precocity.

Other. Macrocranium (24 per cent), mental deficiency (10 per cent), seizures (12 per cent), syndactyly, glaucoma, corneal opacity, potentially malignant melanoma of iris, neurofibromata of bladder. Verrucous nevus. Pheochromocytoma, sexual precocity. Pulmonic stenosis. Vascular hyperplasia of the intima and media; may give rise to renal artery stenosis with consequent hypertension.

NATURAL HISTORY. Often evident in early childhood; 47 per cent of patients develop some neurologic impairment, sometimes secondary to nerve compression as with blindness due to optic nerve pressure. Malignant change occurs in 5 to 10 per cent of cases, most commonly in males.

ETIOLOGY. Autosomal dominant with high penetrance but wide variability in expression. About 50 per cent of patients have a fresh gene mutation, and Crowe, et al.[2] calculated the mutation rate per gamete per generation to be 1×10^{-4}, the highest known for the human.

REFERENCES

1. Von Recklinghausen, F.: Ueber die multiplen Fibroma der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin, A. Hirschwald, 1882.
2. Crowe, F. W., Schull, W. J., and Neel, J. V.: Multiple Neurofibromatosis. American Lecture Series No. 281. Springfield, Ill., Charles C Thomas, 1952.
3. Canale, D., Bebin, J., and Knighton, R. S.: Neurologic manifestations of von Recklinghausen's disease of the nervous system. Confin. Neurol., *24*:359, 1964.
4. Fienman, N. L., and Yakovac, W. C.: Neurofibromatosis in childhood. J. Pediatr., *76*:339, 1970.
5. Weichert, K. A., Dine, M. S., Benton, C., and Silverman, F. N.: Macrocranium and neurofibromatosis. Radiology, *107*:163, 1973.
6. Mena, E., Bookstein, J. J., Holt, J. F., and Fry, W. J.: Neurofibromatosis and renovascular hypertension in children. Am. J. Roentgenol. Radium Ther. Nucl. Med., *118*:39, 1973.



A, Café-au-lait, ovaloid, irregular, and minute pigmentary spots on the trunk of one child and in the axilla – axillary "freckling" – in another child.

B, Pseudofracture of distal tibia and fibula. Hypertrophy of toe, in relation to the hamartomatous process in that area.

McCUNE-ALBRIGHT SYNDROME

(Osteitis Fibrosis Cystica)

Polyostotic Fibrous Dysplasia, Irregular Skin Pigmentation, Sexual Precocity

McCune[1] and Albright, et al.[2] described this condition in 1935 and 1936 respectively. More than 100 cases have been reported. The relative frequency of diagnosis in females vs. males is 3:2.

ABNORMALITIES

Bone. Multiple areas of fibrous dysplasia, most commonly in long bones and pelvis; may also include facial bones causing facial asymmetry. May result in deformity, increased thickness of bone, or both.

Skin. Irregular brown pigmentation, most commonly over sacrum, buttocks, upper spine; unilateral in about 50 per cent of cases.

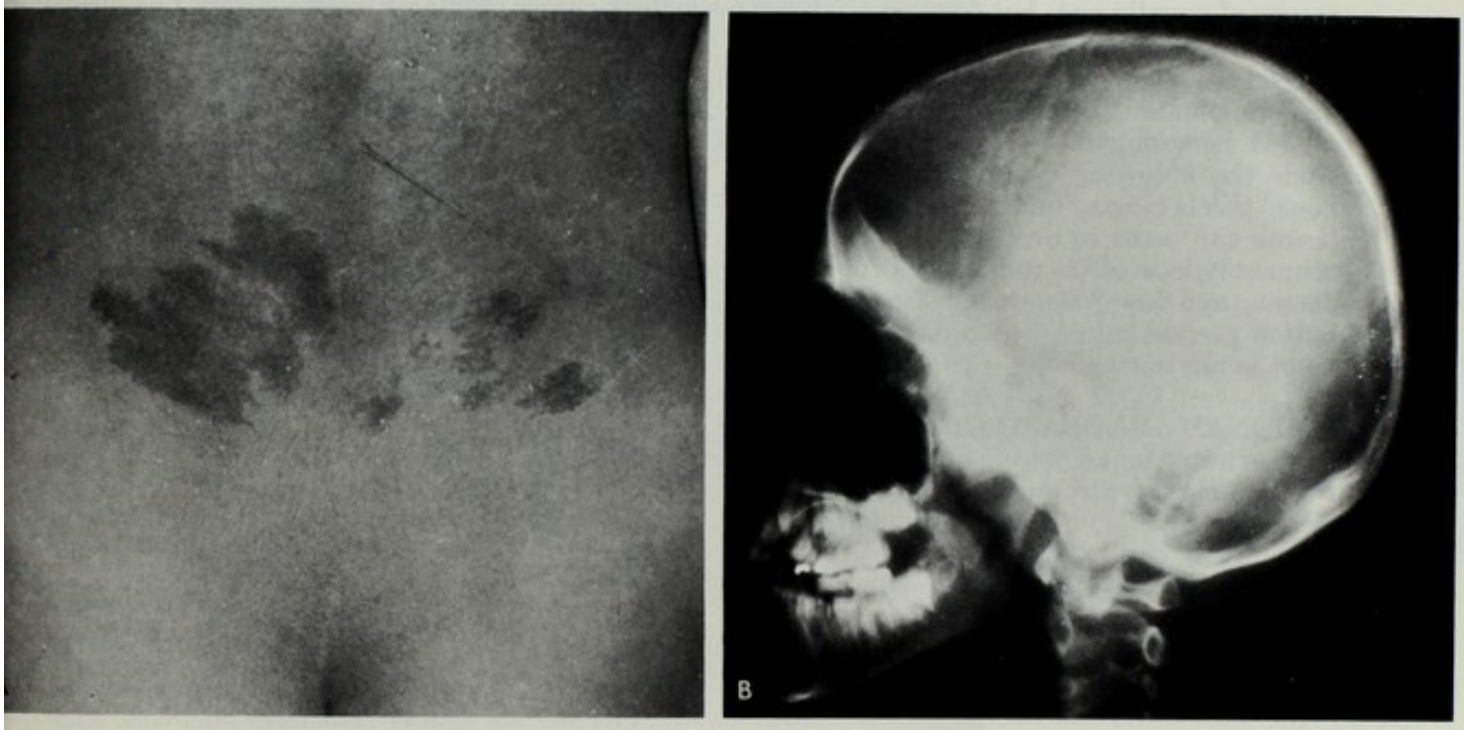
Endocrine. Precocious menarche in female, occasional sexual precocity in male. Occasional instances of basophilic adenoma, acromegaly, hyperthyroidism (19 per cent), hypercalcemia, diabetes mellitus.

NATURAL HISTORY. The pigmentation is usually evident in infancy, and the bone dysplasia may progress during childhood, resulting in deformity, fracture, or both, most commonly in the upper femur. Thickening of bone in the calvarium can lead to cranial nerve compression with such serious consequences as blindness or deafness. The sexual precocity in the female is often unusual in character, with menstruation prior to breast or pubic hair development. The accelerated maturation coincident with sexual precocity may result in early attainment of full stature such that adult height can be relatively short.

ETIOLOGY. The cases have been sporadic occurrences in the families, and the etiology is undetermined.

REFERENCES

1. McCune, D. J.: Osteitis fibrosa cystica. Am. J. Dis. Child., *52*:745, 1936.
2. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Report of five cases. N. Engl. J. Med., *216*:727, 1937.
3. Arlien-Soborg, U., and Iversen, T.: Albright's syndrome. A brief survey and report of a case in a seven year old girl. Acta Paediatr., *45*:558, 1956.



A, Irregular café-au-lait pigmentation over lower back. *B*, Dense thick bone at the base of the skull. From an older girl who had her menarche at the age of four and one-half years.

KLIPPEL-TRENAUNAY-WEBER SYNDROME

Asymmetric Limb Hypertrophy, Hemangiomata

This entity was originally reported by Klippel and Trenaunay in 1900.[1] Parkes-Weber[2] in 1907 added the infrequent finding of arteriovenous fistula. Approximately 140 cases have thus far been published.

ABNORMALITIES

Limbs. Congenital or early childhood hypertrophy of usually one, but occasionally more than one, limb. The hypertrophy may not necessarily coincide with the area of hemangiomatous involvement.

Skin. The hemangiomas vary greatly and include the following types: capillary, cavernous, phlebectasia, and varicosities. These lesions can occur in any area, but are more commonly located on the legs, buttocks, abdomen, and lower trunk. Unilateral distribution predominates, but bilateral involvement is not uncommon.

OCCASIONAL ABNORMALITIES

Limbs. Arteriovenous fistula, lymphangiomatous anomalies, atrophy.

Hands and Feet. Macrodactyly, disproportionate growth of the digits whether large or small, syndactyly, polydactyly, oligodactyly.

Skin. Hyperpigmented nevi and streaks, neonatal and childhood ulcers and vesicles, cutis marmorata, telangiectasia.

Craniofacial. Asymmetrical facial hypertrophy, hemangiomas, microcephaly, macrocephaly, intracranial calcifications, and eye abnormalities such as glaucoma, cataracts, and heterochromia.

Viscera. Visceromegaly, hemangiomas of the intestinal tract, urinary system, mesentery, and pleura, aberrant major vessels, lymphectasia.

Performance. Mental deficiency and/or seizures, usually only in patients having facial hemangiomatosis.

Growth. Small stature, tall stature.

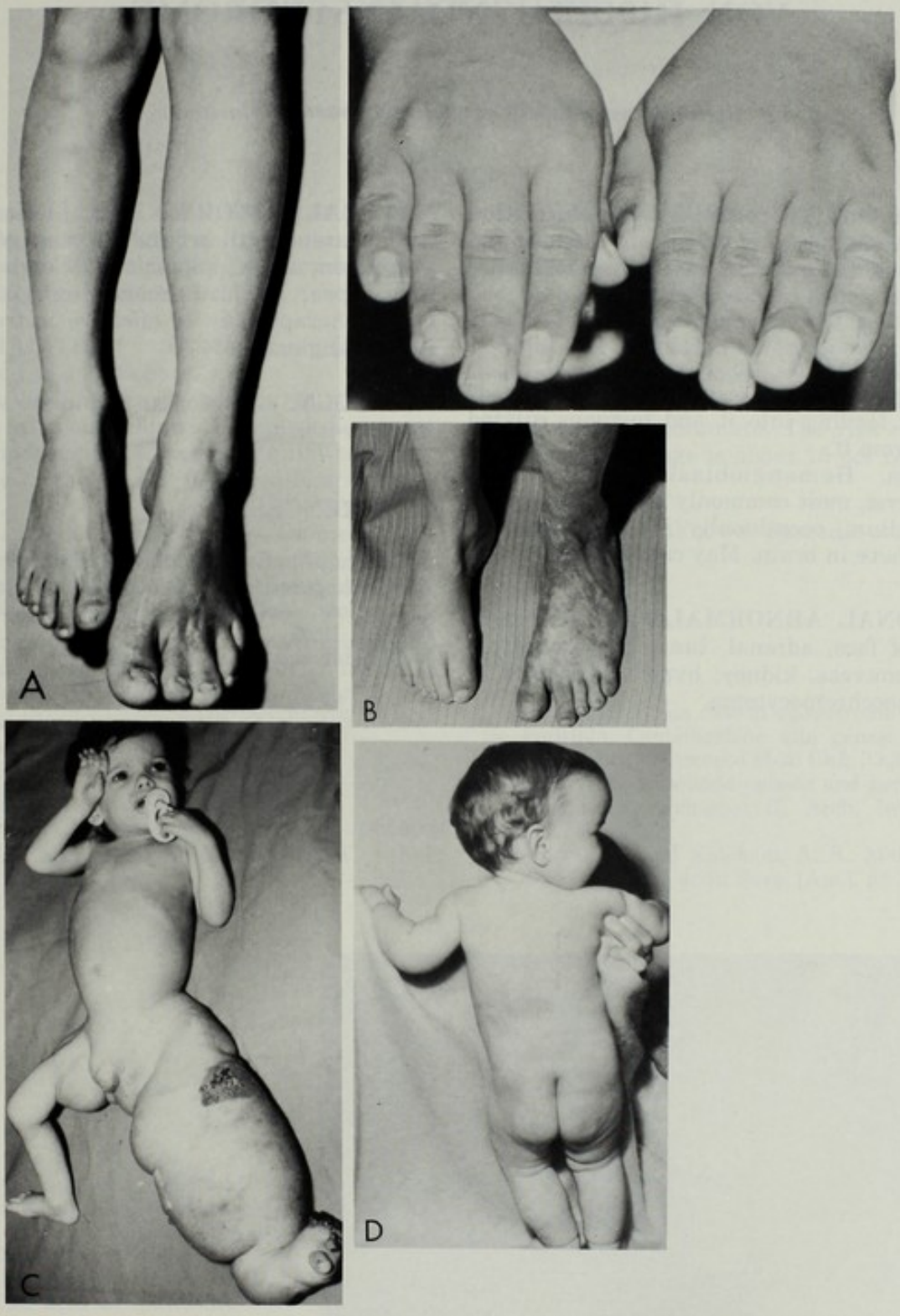
Other. Enlargement of the genitalia, intravascular clotting problems, lipodystrophy.

NATURAL HISTORY. The usual patient with this syndrome does relatively well. There may be disproportionate growth which requires epiphyseal fusion or removal of the appropriate phalanx. Joint discomfort is not uncommon and arthritic-type problems may develop. Leg swelling can be bothersome and ulcers and other chronic skin difficulties may develop. Those few patients with accompanying arteriovenous fistulae require surgical intervention. Rarely, amputation is necessary, particularly if the extremity reaches gigantic proportions or clotting difficulties secondarily occur. Hemangiomas of the viscera, brain, eyes, and other areas should always be looked for in this extremely variable disorder.

ETIOLOGY. Unknown. Sporadic occurrence.

REFERENCES

1. Klippel, M., and Trenaunay, P.: Du naevus variqueux osteo-hypertrophique. Arch. Gen. Med., *185*:641, 1900.
2. Parkes-Weber, F.: Angioma formation in connection with hypertrophy of limbs and hemi-hypertrophy. Br. J. Dermatol., *19*:231, 1907.
3. Lindenauer, S. M.: Congenital arteriovenous fistula and the Klippel-Trenaunay syndrome. Ann. Surg., *174*:248, 1971.
4. Kuffer, F. R., Starzynski, T. E., Girolami, A., Murphy, L., and Grabstald, H.: Klippel-Trenaunay syndrome, visceral angiomatosis, and thrombocytopenia. J. Pediatr. Surg., *3*:65, 1968.
5. Furukawa, T., Igata, A., Toyokura, Y., and Ikeda, S.: Sturge-Weber and Klippel-Trenaunay syndrome with nevus of Ota and Sto. Arch. Dermatol., *102*:640, 1970.
6. Stephan, M. J., Hall, B. D., Smith, D. W., and Cohen, M. M., Jr.: Macrocephaly in association with unusual cutaneous angiomatosis. J. Pediatr., *87*:353, 1975.



A, Fourteen year old showing asymmetrical hypertrophy in legs, hands (note left fifth finger), and feet with abnormal vasculature as was evident in the dorsum of the right foot.

B, Feet of a mentally deficient microcephalic boy showing left-sided hemangiomatous involvement and macrodactyly.

C, Mentally normal girl with involvement of clitoris, right thigh, and severely so in left leg with secondary intravascular clotting. The left leg was amputated, plastic surgery was done in the other involved areas, and the patient is vastly improved.

D, Mentally normal girl with macrocephaly and hemangiomata in left trunk and lower limb.

VON HIPPEL-LINDAU SYNDROME

Retinal Angiomata, Cerebellar Hemangioblastoma

Lindau,[1] in 1926, recognized this association of angiomatous retina (von Hippel's disease) and angiomatous tumors of the cerebellum and other parts of the central nervous system.

ABNORMALITIES

Eye. Angioma, often peripheral, with "beaded" artery leading into it and tortuous dilated vein from it.

Cerebellum. Hemangioblastoma, sometimes with cyst, most commonly in cortical area of cerebellum, occasionally in spinal cord or elsewhere in brain. May calcify.

OCCASIONAL ABNORMALITIES. Hemangiomata of face, adrenal, lung, liver; multiple cysts of pancreas, kidney; hypernephromata of kidney; pheochromocytoma.

NATURAL HISTORY. Retinal lesions usually not apparent until around 25 years of age with subsequent visual impairment. Cerebellar signs may appear in third decade. Light coagulation or cryotherapy may be effective in treating the retinal angiomata.

ETIOLOGY. Autosomal dominant with varying expression.

REFERENCES

1. Lindau, A.: Studien über Kleinhirnsystem. Bon Pathogenese und Beziehungen zur Angiomatosis retinae. Acta Path. Microbiol. Scand. [Suppl.], *1*:1, 1926.
2. Christoferson, L. A., Gustafson, M. B., and Petersen, A. G.: Von Hippel-Lindau's disease. J.A.M.A., *178*:280, 1961.

MAFFUCCI SYNDROME

Enchondromatosis, Hemangiomata

Maffucci[1] in 1881 described a patient with dyschondroplasia and multiple cutaneous hemangiomas. More than 80 similar cases have subsequently been recroded.

ABNORMALITIES[2, 3] Onset from the neonatal period to adolescence.

Skeletal. Variable early bowing of the long bones with asymmetrical retarded growth. Enchondromata (40 per cent unilateral) primarily in the hands, feet, and long tubular bones.

Vascular. Hemangiomata, most frequently located in the dermis and subcutaneous fat adjacent to the areas of enchondromatosis, but may occur anywhere. Types of hemangiomata are capillary, cavernous, and especially phlebectatic, often having a grape-like appearance. Thrombosis of the dilated blood vessels with phlebolith formation occurs in 43 per cent of cases.

OCCASIONAL ABNORMALITIES. Lymphangiectasis, hemangiomas of the mucous membranes and gastrointestinal tract, other tumors.

NATURAL HISTORY. The patients usually appear normal at bith but within the first four years hemangiomata appear, 25 per cent during the first year. Subsequent enchondromata formation is noted by adolescence. The disorder can be mild, but it is often severe enough to require multiple surgical procedures and occasionally amputation. About 26 per cent have fractures, related to enchondromata. The risk of chondrosarcomatous change is about 15 per cent.

ETIOLOGY. Unknown. Sporadic occurrence.

REFERENCES

1. Maffucci, A.: Di un caso di encondroma ed angioma multiplo: Contribuzione alla genesi embrionale dei tumor. Movimento Med. Chir., *3*:399, 1881.
2. Bean, W. B.: Dyschondroplasia and hemangiomata (Maffucci's syndrome) II. Arch. Intern. Med., *102*:544, 1958.
3. Lewis, R. J., and Ketcham, A. S.: Maffucci's syndrome. J. Bone Joint Surg. [Am.], *55*:1465, 1973.



Note the enlarged right foot and the vascular lesions. These pictures were taken just following the removal of this man's right arm because of chondrosarcomatous change in an area of enchondromata. He had also had gastrointestinal bleeding episodes secondary to lower intestinal hemangiomata.

OSTEOCHONDROMATOSIS SYNDROME

(Ollier's Disease, Enchondromatosis)

Asymmetric Enchondromata with Local Growth Deficiency

Ollier[1] described this disorder in 1899 and well over 100 cases have been reported.

ABNORMALITIES

Skeletal. Rounded masses of hyaline cartilage lead to fan-like radiolucencies in metaphyses, later diaphyses, and sometimes epiphyses. Usually asymmetric with limited growth of affected bones. Most commonly tubular long bones, sometimes pelvis.

NATURAL HISTORY. Asymmetric growth usually first noted at one to four years of age with little progression after adolescence. Liable to fracture and there is a risk (10 per cent?) of chondrosarcoma developing.

ETIOLOGY. Unknown. Usually sporadic, but does rarely occur in more than one member of a family.

REFERENCES

1. Ollier, L.: De la Dyschondroplasia. Bull. Soc. Chir. (Lyon), *3*:22, 1899.
2. Margolis, J.: Ollier's disease. Arch. Intern. Med., *103*:279, 1959.



Six year old and roentgenogram of her left tibia. She had onset of leg shortness at two years of age. By 16 years of age she had suffered several fractures of the left leg and had developed scoliosis.

PEUTZ-JEGHERS SYNDROME

Mucocutaneous Pigmentation, Intestinal Polyposis

In 1896 Hutchinson[1] described the pigmentary changes in an individual who later died with intussusception. Peutz[2] clearly set forth the disease in 1921, and Jeghers, et al.[3] further established this disease entity in 1949. More than 180 cases have been documented.

ABNORMALITIES

Pigmentation. Vertical bands of epidermal pigment presenting as blue-gray or brownish spots in lips, buccal mucous membrane, perioral area, and sometimes digits and elsewhere.

Polyposis. Hamartomatous muscularis mucosae polyps in jejunum, sometimes in other mucous secreting intestinal mucosa, and occasionally in nasopharynx, bladder, bronchial mucosa.

Other Tumors. Rare granulosa cell tumor of ovary.

NATURAL HISTORY. The pigmentary spots appear from infancy through early childhood and tend to fade in the adult. Seventy per cent of patients have some gastrointestinal problem by age 20 years, most commonly colicky abdominal pain (60 per cent), intestinal bleeding (25 per cent), or both. Intussusception, which may spontaneously recede, is the most serious complication, and iron deficiency anemia may result from chronic blood loss. There is a definite but low risk of malignant transformation in the polyps, with carcinoma of the jejunum, duodenum, and stomach having been reported. Clubbing of the fingers may occasionally occur in this disease.

ETIOLOGY. Autosomal dominant with a high degree of penetrance.

REFERENCES

1. Hutchinson, J.: Pigmentation of the lips and mouth. Arch. Surg., *7*:290, 1896.
2. Peutz, J. L. A.: Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentation of skin and mucous membrane. Ned. Maanschr. Geneesk., *10*:134, 1921.
3. Jeghers, H., McKusick, V. A., and Katz, K. H.: Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. A syndrome of diagnostic significance. N. Eng. J. Med., *241*:993, 1949.
4. Bartholomew, L. G., Moore, C. E., Dahlin, D. C., and Waugh, J. M.: Intestinal polyposis associated with mucocutaneous pigmentation. Surg. Gynecol. Obstet., *115*:1, 1962.
5. Papaioannou, A., and Critselis, A.: Malignant changes in Peutz-Jeghers syndrome. N. Engl. J. Med., *298*:694, 1973.



Spotty pigmentation of lips and periorbital area in a child with intestinal polyps. (From Sheward, J. D.: Brit. Med. J., *1*:921, 1962.)

GARDNER SYNDROME

Polyposis of Colon, Epidermal Cysts, Osteomas

Gardner and Richards[1] set forth a complete evaluation of this disease in 1953. The hamartomatous lesions generally do not become evident until latter childhood. More than 100 cases have been reported.

ABNORMALITIES

Intestine. Adenomatous polyps of colon, rectum, and occasionally stomach and small intestine.

Skin. Epidermal inclusion and/or sebaceous cysts, especially on back, scalp, face. Sometimes fibromas, invasive desmoid, or both.

Bone. Osteomata of calvarium, mandible, face, elsewhere, leading to bone deformation, cortical thickening.

Dental. Dentigerous cysts, supernumerary teeth, delayed eruption of teeth.

OCCASIONAL ABNORMALITIES. Other hamartomata, including odontoma, leiomyoma, lipoma, trichoepithelioma, neurofibroma, thyroid carcinoma and polyps of stomach and small intestine. Scoliosis.

NATURAL HISTORY. Hamartomata usually become evident between ten and 20 years of age; thereafter there is grave danger of malignant change in the colonic adenomata, with the majority of affected individuals developing carcinoma of the colon between 19 and 50 years of age. The risk is of sufficient magnitude to warrant prophylactic colectomy in late childhood. Mesenteric fibromatosis and severe adhesions represent potential postoperative problems.

ETIOLOGY. Autosomal dominant with high degree of penetrance.

REFERENCES

1. Gardner, E. J., and Richards, R. C.: Multiple cutaneous and subcutaneous lesions occurring simultaneously with herditary polyposis and osteomatosis. Am. J. Hum. Genet., *5*:139, 1953.
2. Weary, P. E., Linthicum, A., Cawley, E. P., Coleman, C. C., and Graham, G. F.: Gardner's syndrome. A family group study and review. Arch. Dermatol., *90*:20, 1964.
3. Leichtling, J. J.: Gardner's syndrome. Mt. Sinai J. Med. N.Y., *38*:311, 1971.

OSLER HEMORRHAGIC TELANGIECTASIA SYNDROME

(Hereditary Hemorrhagic Telangiectasia)

Epistaxes, Multiple Telangiectases

This entity was set forth in 1901 by Osler.[1] The telangiectases contain dilated vessels having only an endothelial wall with no elastic tissue and a tendency toward arteriovenous fistuli. Over 264 affected families have been reported, and the incidence is about 1:50,000.

ABNORMALITIES

Vessels. Pinpoint, spider, and/or nodular telangiectases most commonly on tongue, mucosa of lips, face, conjunctiva, ears, fingertips, nail beds, and nasal mucous membrane; occasionally in gastrointestinal tract, bladder, vagina, uterus, lungs, liver, and/or brain.

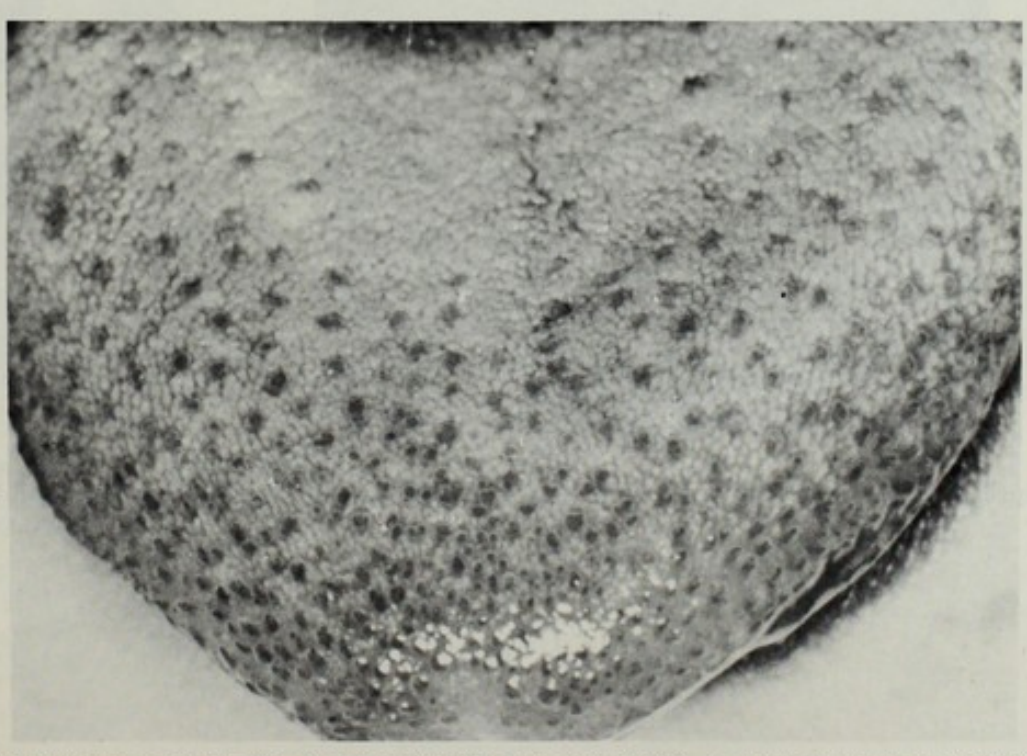
OCCASIONAL ABNORMALITIES. Arteriovenous fistulas in lung, cirrhosis of liver, cavernous angiomata, port wine stain, and aneurysms. Vascular anomalies in brain.

NATURAL HISTORY. Epistaxes often occur in childhood, and the telangiectases become apparent in latter childhood and tend to enlarge, giving rise to increased frequency of hemorrhage. Intermittent brain hemorrhages may give rise to seizures, transient hemipareses, visual disturbances, and/or speech problems. Generally aggravated by pregnancy.

ETIOLOGY. Autosomal dominant with varying expression.

REFERENCES

1. Osler, W.: On a family form of recurring epistaxis, associated with multiple telangiectases of skin and mucous membrane. Bull. Hopkins Hosp., *12*:333, 1901.
2. Bird, R. M., Hammarsten, J. F., Marshall, R. A., and Robinson, R. R.: Family reunion: study of hereditary hemorrhagic telangiectasia. N. Engl. J. Med., *257*:105, 1957.
3. Schaumann, B., and Alter, M.: Cerebrovascular malformations in hereditary hemorrhagic telangiectasia. Minn. Med., *56*:951, 1973.



Small telangiectases in the tongue of a girl who presented with cyanotic plethora secondary to multiple arteriovenous fistulae in the lung.

MULTIPLE NEUROMA SYNDROME

Multiple Neuromata of Tongue, Lips, +/− Medullary Thyroid Carcinoma, +/− Pheochromocytoma

More than 20 cases of this disorder have been recognized.[1, 2]

ABNORMALITIES[1, 2]

Growth. Tend toward arachnodactyly, pes cavus, +/− kyphoscoliosis.

Mucosal Neuromata, Neurofibromata. Prominent lips, nodular tongue, thickened anteverted eyelids, +/− involvement of nasal, laryngeal, and intestinal mucous membranes (which may result in malabsorbtion).

Other Tumors. Medullary thyroid carcinoma, pheochromocytoma.

Other. Tendency toward coarse-appearing facies.

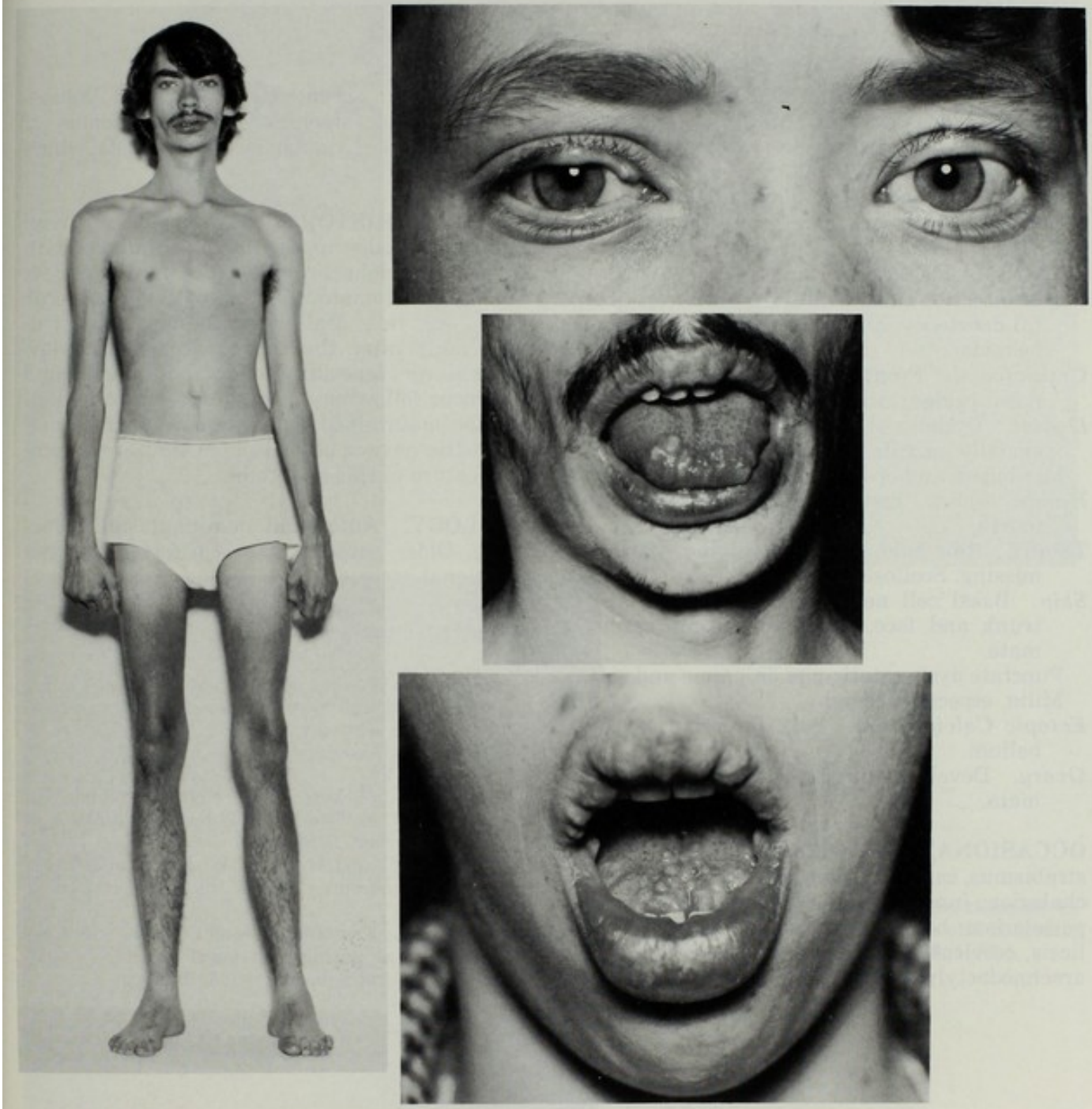
OCCASIONAL ABNORMALITIES. Cornea: Slit lamp examination may reveal medullated nerve fibers. Cutaneous neuromata and/or neurofibromata. Parathyroid hyperplasia, possibly secondary to calcitonin effect from medullary thyroid carcinoma.

NATURAL HISTORY. Oral neuromata are usually evident in childhood with medullary thyroid carcinoma and/or pheochromocytoma becoming serious risks (? about 50 per cent for each) after adolescence. When medullary thyroid carcinoma is implicated a total thyroidectomy should usually be done because the lesion is often multicentric, and when pheochromocytoma is implicated a thorough exploration should be accomplished since it is often bilateral and may also be extra-adrenal.

ETIOLOGY. Autosomal dominant inheritance with variable expression is implied, with the majority of cases presumed to be fresh mutations.

REFERENCES

1. Schimke, R. N., Hartmann, W. H., Prout, T. E., and Rimoin, D. L.: Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma and multiple neuromas. N. Engl. J. Med., *279*:1, 1968.
2. Gorlin, R. J., Sedano, H. O., Vickers, R. A., and Cervenka, J.: Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid – a syndrome. Cancer, *22*:293, 1968.



Left, Note the slim asthenic habitus.
Right, Multiple neuromata involving conjunctiva, tongue, and contributing to the prominent lips. (Courtesy of A. B. Hayles, Mayo Clinic.)

BASAL CELL NEVUS (CARCINOMA) SYNDROME

Basal Cell Nevi, Broad Facies, Rib Anomalies

Though this condition had been previously described, it was not until 1951 that the broad extent of this pattern of altered morphogenesis was set forth by Binkley and Johnson.[1] Subsequently more than 200 cases have been reported.[2, 3]

ABNORMALITIES

Performance. Variable mild to moderate mental deficiency, aberrant neurologic function, behavior.

Craniofacial. Frontoparietal bossing. Broad nasal bridge, mild prognathism.

Dental. Dyskeratotic cysts of mandible, occasionally maxilla.

Misshapen and/or carious teeth.

Hands. Short metacarpals, especially the fourth.

Thorax. Ribs bifid, synostotic, and/or partially missing. Scoliosis.

Skin. Basal cell nevi over neck, upper arms, trunk and face, prone to become carcinomata.

Punctate dyskeratotic pits on palms and soles.

Milia, especially facial.

Ectopic Calcification. Falx cerebri, falx cerebellum.

Ovary. Development of calcified ovarian fibromata.

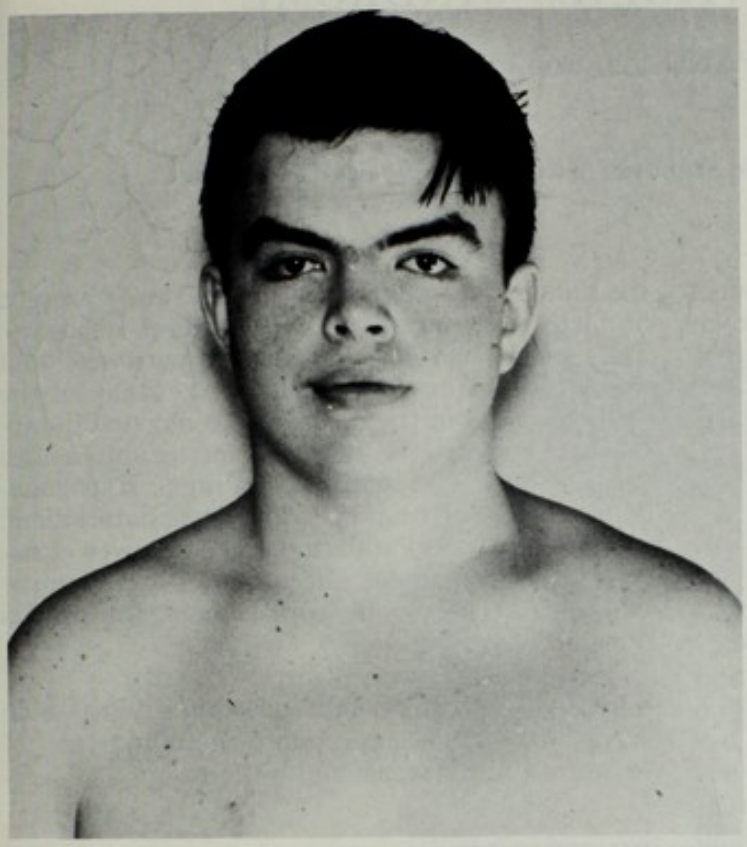
OCCASIONAL ABNORMALITIES. Internal strabismus, cataract, coloboma of iris, glaucoma, chalazion, inner canthal folds, telecanthus, hypertelorism; bony bridging of sella turcica, scoliosis, cervical and/or thoracic vertebral fusion, arachnodactyly; hydrocephalus, small genitalia, hypogonadism, cryptorchidism. Medulloblastoma, fibromas, lipomas or neurofibromas of skin. Anosmia. Lymphomesenteric cysts which tend to calcify.

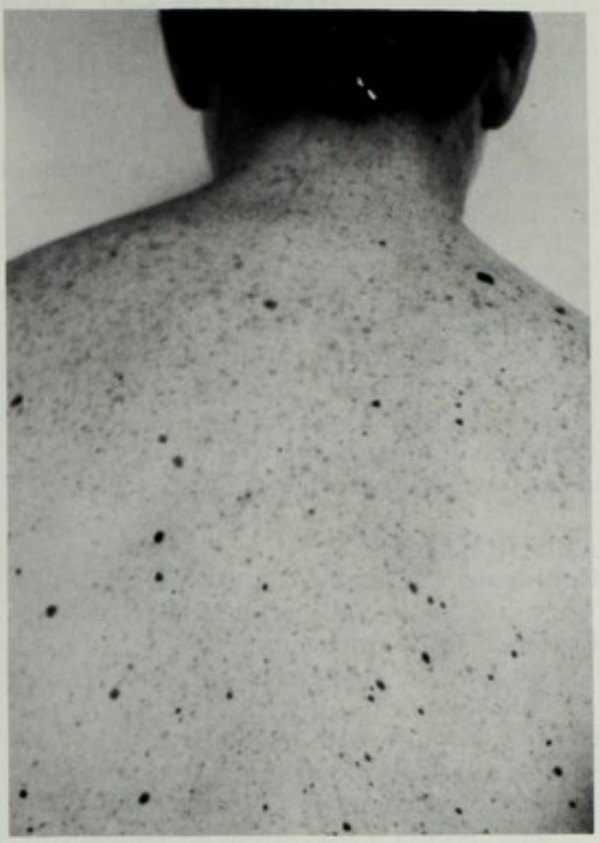
NATURAL HISTORY. The basal cell nevi nodules gradually appear during childhood with increase at adolescence. On the face the nevi may be papillomatous and are likely to occur around the lids. Malignant change is particularly likely after the second decade. The jaw cysts enlarge, especially in latter childhood, and may recur following curettage. A constant vigil must be maintained for malignant transformation of the nevi or other tumors that are a common feature of this syndrome.

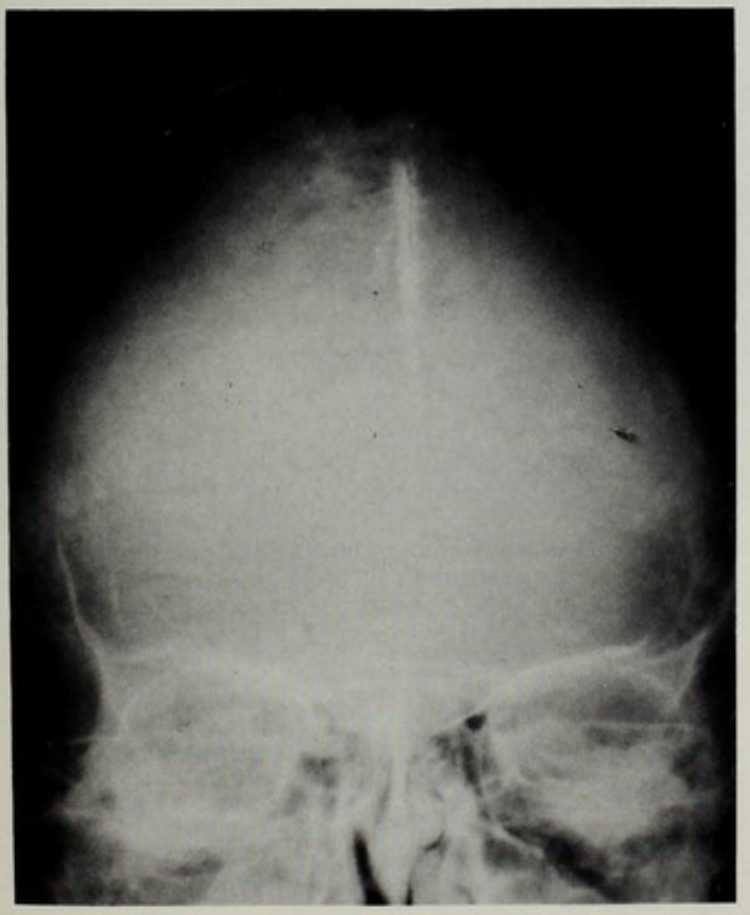
ETIOLOGY. Autosomal dominant, full penetrance. Older paternal age is a factor in fresh mutational cases.

REFERENCES

1. Binkley, G. W., and Johnson, H. H., Jr.: Epithelioma adenoides cysticum: Basal cell nevi, agenesis of the corpus callosum and dental cysts. A clinical and autopsy study. Arch. Dermatol., *63*:73, 1951.
2. Gorlin, R. J., Vickers, R. A., Kellen, E., and Williamson, J. J.: The multiple basal-cell nevi syndrome. Cancer, *18*:89, 1965.
3. Ferrier, P. E., and Hinrichs, W. L.: Basal-cell carcinoma syndrome. Am. J. Dis. Child., *113*:538, 1967.
4. Codish, S. D., Kraszeski, J., and Pratt, K.: CNS developmental anomaly in basal cell nevus syndrome. Neuropaediatrie, *4*:338, 1973.







Fifteen year old. Note mineralization in falx cerebri. (From Ferrier, P. E., and Hinrichs, W. L.: Am. J. Dis. Child., *113*:538, 1967.)

MULTIPLE LENTIGINES SYNDROME

(LEOPARD Syndrome)

Multiple Lentigines, Pulmonic Stenosis, Mild Hypertelorism, Deafness

Gorlin, et al.[1] recognized the multiple defect nature of this disorder and utilized the acronym LEOPARD syndrome to denote the Lentigines, EKG abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness. More than 30 cases have been described.[1-3]

ABNORMALITIES

Cutaneous. Multiple 1- to 5-mm dark lentigines, especially on neck and trunk.

Cardiac. Mild pulmonic stenosis. Electrocardiographic changes of prolonged P-R and QRS, abnormal P waves.

Other. Mild growth deficiency, mild ocular hypertelorism, prominent ears, mild to moderate sensorineural deafness, winged scapulae, pectus excavatum or carinatum, and late adolescence.

OCCASIONAL ABNORMALITIES. Mental deficiency, mandibular prognathism, café-au-lait spots, unilateral renal and/or gonadal agenesis or hypoplasia, hypogonadism, hypospadias, hyposmia, subaortic stenosis.

NATURAL HISTORY. Lentigines differ from freckles in being darker of color, usually present at birth and not related to sunlight exposure. They often increase in number with age and may occur in any cutaneous area. Many of the other features of the disorder are not readily apparent and must be searched for; examples are the deafness and cardiac findings. Hypogonadism may be secondary to hypogonadotrophism; hence these individuals should be followed closely at the age of adolescence in order to determine whether sex hormone replacement therapy is merited.

ETIOLOGY. Autosomal dominant with wide variability in the expression, including lack of lentigines in an occasional patient.

REFERENCES

1. Gorlin, R. J., Anderson, R. C., and Blaw, M.: Multiple lentigenes syndrome. Am. J. Dis. Child., *117*:652, 1969.
2. Sommer, A., Contras, S. G., Graenen, J. M.,and Hosier, D. M.: A family study of the leopard syndrome. Am. J. Dis. Child., *121*:520, 1971.
3. Swanson, S. L., Santen, R. J., and Smith, D. W.: Multiple lentigines syndrome. J. Pediatr., *78*:1037, 1971.



Adolescent boy showing lentigines, prominent ears, and mild ocular hypertelorism. (From Gorlin, R. J., et al.: Am. J. Dis. Child., *117*:652, 1969.)

GOLTZ SYNDROME

Poikiloderma with Focal Dermal Hypoplasia, Syndactyly, Dental Anomalies

This mesoectodermal disorder was well recognized as a concise entity by Goltz et al.[1] in 1962, although well described cases had been reported prior to that time. More than 50 cases have been documented.

ABNORMALITIES[1-5]

Skin. Linear areas of hypoplasia with altered pigmentation, telangiectasis, lipomatous nodules projecting through localized areas of skin atrophy.

Angiofibromatous nodules around lips and anus.

Nails. Dystrophic nails, narrow and/or hypoplastic.

Teeth. Hypoplasia of teeth, enamel hypoplasia, late eruption, and/or irregular placement.

Extremities. Syndactylism of fingers and/or toes, especially third and fourth fingers.

Eyes. Strabismus, coloboma, and/or microphthalmos.

OCCASIONAL ABNORMALITIES. Moderate short stature, joint hypermotility, mental retardation, microcephaly, bulbar angiofibroma of eye, partial alopecia, congenital heart defects, hernia, skeletal asymmetry, scoliosis, hypoplasia or aplasia of clavicle, failure of pubic bone fusion, polydactyly, adactyly, hypoplasia of digit, cleft hand.

NATURAL HISTORY. The skin lesions are usually present at birth, although the skin lipomata and the lip and anal papillomata may develop later. No effective therapy is known except plastic surgery for the syndactyly and removal of papillomata when indicated.

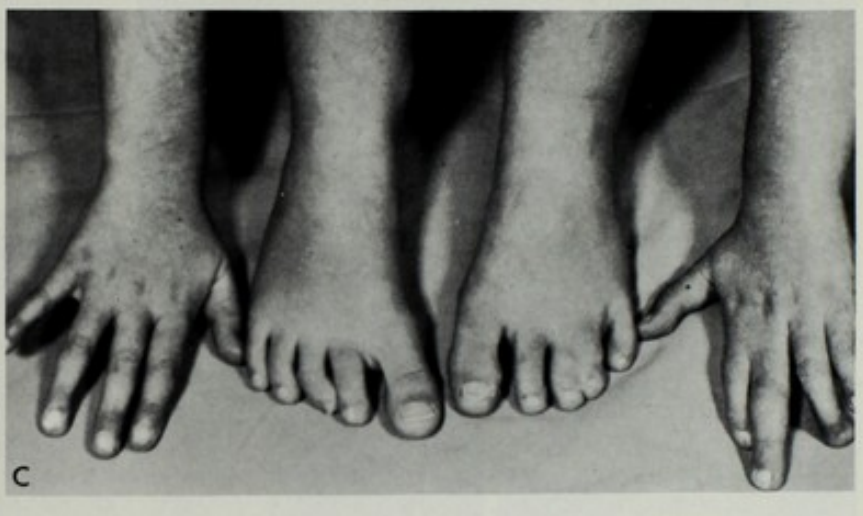
ETIOLOGY. Wodniansky[4] reported partial expression in the mother and sibling of a patient. All other cases have been sporadic. The majority of cases have been females. The present hypothesis is that this is a single gene effect, usually lethal in the male, and most cases represent fresh mutations, a similar situation to incontinentia pigmenti. There are many similarities between incontinentia pigmenti and Goltz syndrome, and it is tempting to consider the possibility that both diseases represent genetic alterations of a similar system.

REFERENCES

1. Goltz, R. W., Peterson, W. C., Gorlin, R. J., and Ravits, H. G.: Focal dermal hypoplasia. Arch. Dermatol., *86*:708, 1962.
2. Gorlin, R. J., Meskin, L. H., Peterson, W. C., and Goltz, R. W.: Focal dermal hypoplasia syndrome. Acta Dermatovener. (Stockholm), *43*:421, 1963.
3. Holden, J. D., and Akers, W. A.: Goltz's syndrome: focal dermal hypoplasia. A combined mesoectodermal dysplasia. Am. J. Dis. Child., *114*:292, 1967.
4. Wodniansky, P.: Über die Formen der congenitalen Poikilodermie. Arch. Klin. Exp. Dermatol., *205*:331, 1957.
5. Jenner, M.: Naeviforme, Poikilodermie–artige Hautveränderungen mit Missbildungen (Schwimmhautbildungen an den Fingern, Papillome am Anus). 2 bl. Hautkr., *27*:468, 1928.









A, Eleven year old girl.

B, Late eruption of teeth with dental hypoplasia and malformation.

C, Note the syndactyly of the left hand and foot.

D, Thigh, showing irregular areas of altered pigmentation and of fatty herniation through loci of focal dermal hypoplasia (arrow).

DYSKERATOSIS CONGENITA SYNDROME

Hyperpigmentation of Skin, Leukoplakia, Nail Dystrophy, Pancytopenia

Cole originally described this condition in 1930 and recently summarized the findings. Only about 13 cases have been reported.[1-3]

ABNORMALITIES. Although hyperpigmentation of the skin may be present from birth, most of the abnormalities become apparent between five and 15 years of age. Growth deficit is mentioned, but poorly documented.

Skin. Irregular reticular brownish-gray pigmentation with patchy atrophic areas of hypopigmentation.

Hyperkeratosis and hyperhidrosis of palms and soles.

May have bullae, telangiectasis.

Mucous Membranes. Premalignant leukoplakia may be found on lips, mouth, anus, urethra, conjunctiva.

Eyes. Blepharitis, ectropion, and nasolacrimal obstruction with excessive tearing.

Nails. Dystrophy which may progress to absence of nail.

Teeth. Carious, malaligned.

Hair. Tends to be sparse and fine, occasionally premature graying.

Hematologic. Pancytopenia.

Bone. Coarse trabeculation (osteoporosis?) is mentioned, possibly with relative fragility.

Gonad. Testicular hypoplasia.

Other. Partial stenosis of esophagus with dysphagia.

Mental deficiency was noted in two cases.

Hepatic cirrhosis has been detected in at least two cases.

NATURAL HISTORY. The problem in affected tissues tends to become more severe with age, and most patients die before the fourth decade as a consequence of either pancytopenia or malignant transformation in mucous membranes. When present, leukoplakic lesions should be excised as representing premalignant change.

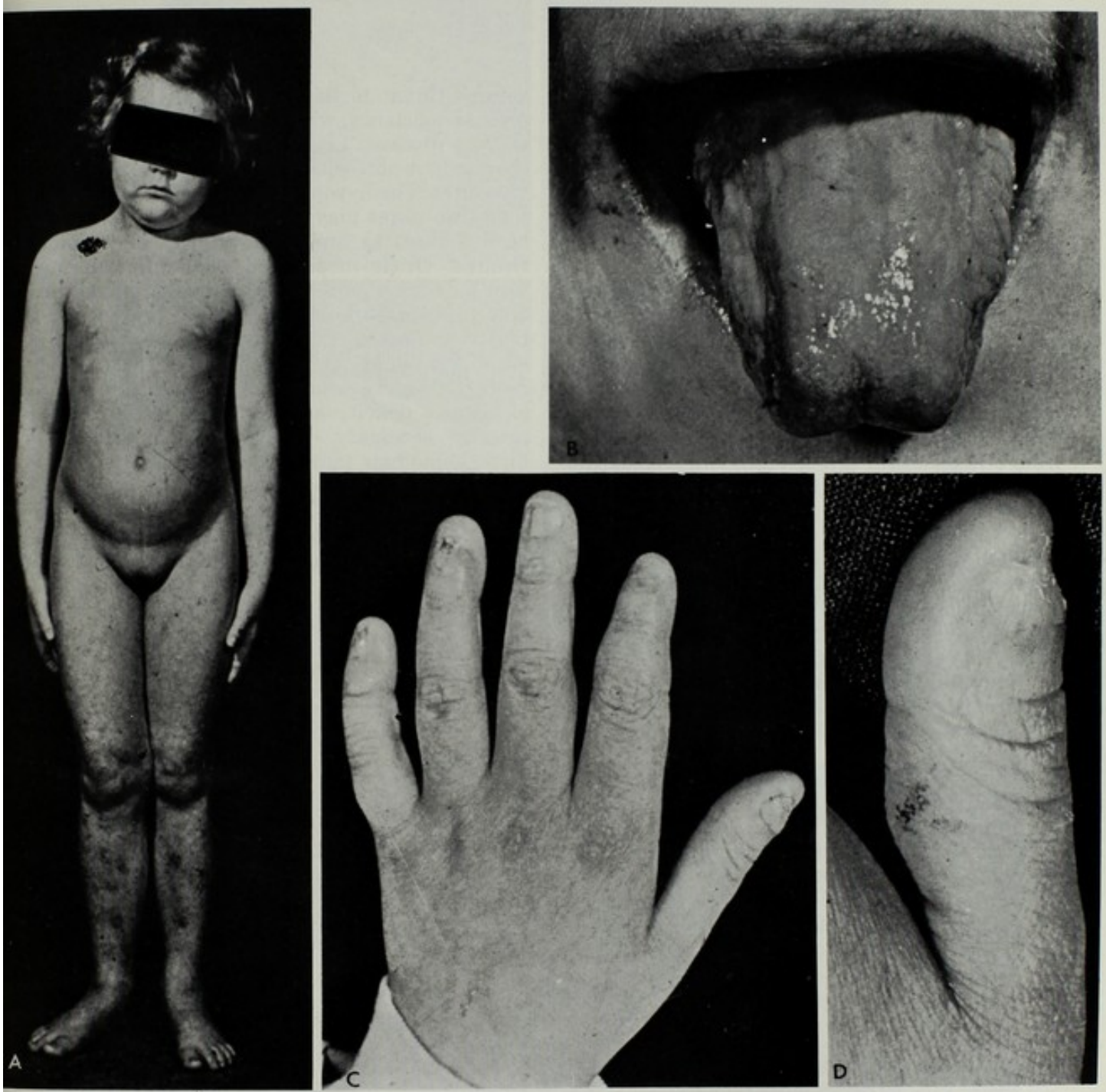
ETIOLOGY. Austosomal recessive determination is implied by a 50 per cent incidence of parental consanguinity and occurrence of affected siblings in three families. Only two of the 13 patients have been females, a finding which is presently unexplained.

COMMENT. The dermatologic term dyskeratosis congenita obviously depicts only one feature of this abiotrophic type of disease with hamartomatous features in which the affected individual develops hypoplasia and dysplasia in the skin, mucous membranes, marrow, and other tissues. The sibling of one patient and the niece of another patient died of leukemia, the latter case raising the question of whether there may be an increased likelihood of leukemia in the heterozygote carrying this mutant gene.

Considering the total pattern of abnormality, dyskeratosis congenita is clearly a different entity from the Fanconi syndrome of pancytopenia with congenital malformations.

REFERENCES

1. Cole, H. N., Cole, H. N., Jr., and Lascheid, W. P.: Dyskeratosis congenita. Relationship to poikiloderma atrophicans vasculare and to aplastic anemia of Fanconi. Arch. Derm., *76*:712, 1957.
2. Georgouras, K.: Dyskeratosis congenita. Aust. J. Derm., *8*:36, 1965.
3. Addison, J., and Rice, M. S.: The association of dyskeratosis congenita and Fanconi's anemia. Med. J. Aust., *1*:797, 1965.



Eight year old patient showing reticulated skin pigmentation *(A)*, smooth tongue without leukoplakia as yet *(B)*, and nail hypoplasia to aplasia *(C* and *D)*. (Courtesy of K. Georgouras, Sydney, Australia.)

HYPOHIDROTIC ECTODERMAL DYSPLASIA SYNDROME

Defect in Sweating, Alopecia, Hypodontia

Thurman[1] described this entity in 1848. In 1875, Charles Darwin[2] set forth the following concise commentary about this disease: "I may give an analogous case, communicated to me by Mr. W. Wedderhorn of a Hindoo family in Scinde, in which ten men, in the course of four generations, were furnished, in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have very little hair on the body, and became bald early in life. They also suffer much during hot weather from excessive dryness of the skin. It is remarkable that no instance has occurred of a daughter being thus affected." In 1929, Weech[3] clearly separated this condition from other clinical problems having ectodermal dysplasia as a feature. Over 130 cases had been reported by 1956.

ABNORMALITIES

Skin. Thin and hypoplastic with decreased pigment and tendency toward papular changes on face and thin, wrinkled eyelids.

Skin Appendages. Hair: fine, dry, and hypochromic; sparse to absent.

Sweat glands: hypoplasia to absence of eccrine glands, apocrine glands more normally represented.

Sebaceous glands: hypoplasia to absence.

Mucous Membranes. Hypoplasia with absence of mucous glands in oral and nasal membranes. Mucous glands may also be absent from bronchial mucosa.

Teeth. Hypodontia to adontia. Anterior teeth tend to be conical in shape.

Craniofacial. Low nasal bridge, small nose with hypoplastic alae nasi, full forehead, prominent supraorbital ridges. Prominent lips.

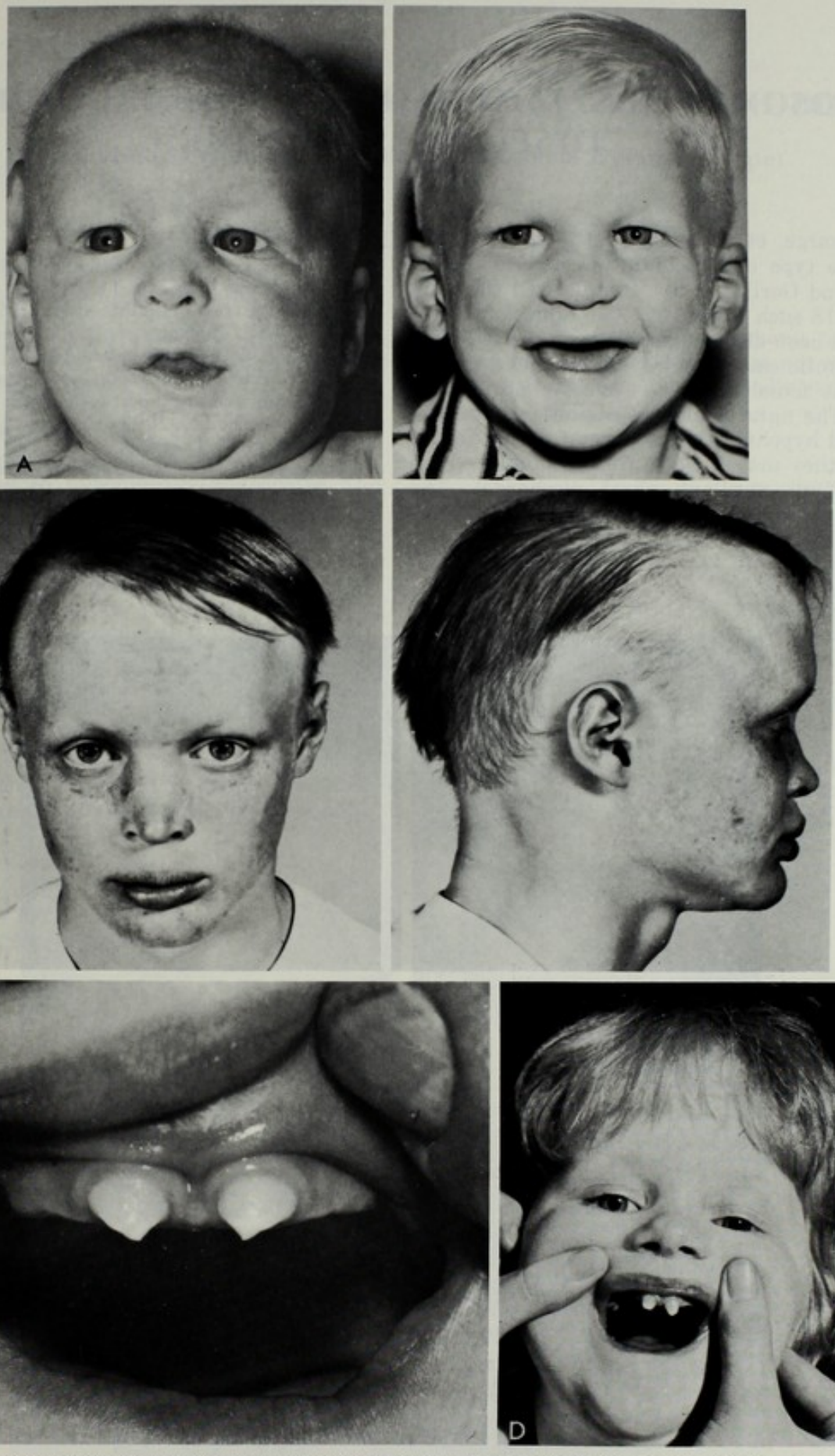
OCCASIONAL ABNORMALITIES. Hoarse voice, hypoplasia to absence of mammary glands and/or nipples, absence of tears, failure to develop nasal turbinates, mild to moderate nail dystrophy, eczematous change in skin, asthmatic symptoms.

NATURAL HISTORY. Hyperthermia as a consequence of inadequate sweating is not only a serious threat to life, but may be the cause of mental deficiency, which is an occasional feature of this disease. Living in a cool climate and cooling by water when overheated are important measures. The hypoplasia of mucous membranes plus thin nares may require frequent irrigation of the nares to limit the severity of purulent rhinitis. Otitis media and lung infection may also be consequences of the mucous membrane defect. Mucous glands have not only been hypoplastic to absent in the respiratory tract but in esophageal and colonic mucosa as well. Early roentgenologic evaluation may reveal the extent of dental deficit, and artificial dentures are usually necessary. Though often hairless at birth, some hair may develop. For cosmetic purposes a wig may merit consideration.

ETIOLOGY. X-linked. Previous reports indicated that about 10 per cent of presumed heterozygous females show some overt expression. Utilizing direct visualization of dermal ridge sweat pores, Frias and Smith noted a diminished frequency of sweat pores in five of six heterozygous mothers of affected males, the latter having an absence of sweat pores. Therefore the majority of heterozygous females show some expression for the disease.

REFERENCES

1. Thurman, J.: Two cases in which the skin, hair and teeth were very imperfectly developed. Medico-Chir. Trans., *31*:71, 1848.
2. Darwin, C.: The Variations of Animals and Plants under Domestication, 2nd ed. London, John Murray, 1875.
3. Weech, A. A.: Hereditary ectodermal dysplasia (congenital ectodermal defect). A report of two cases. Am. J. Dis. Child., *37*:766, 1929.
4. Lowry, R. B., Robinson, G. C., and Miller, J. R.: Hereditary ectodermal dysplasia. Symptoms, inheritance patterns, differential diagnosis, management. Clin. Pediat., *5*:395, 1966.
5. Frias, J. L., and Smith, D. W.: Diminished sweat pores in hypohidrotic ectodermal dysplasia: A new method for assessment. J. Pediatr., *72*:606, 1968.



A, Young infant; diagnosis made after hyperthermic episode. Same boy at two years of age.

B, Older boy. The hypoplasia of the skin contributes to the prominent appearance of the lips. Note the mid-facial hypoplasia.

C, Hypoplasia of alveolar ridge in two year old. Hypoplastic conical incisors.

D, Partial expression in a female.

AUTOSOMAL RECESSIVE HYPOHIDROTIC ECTODERMAL DYSPLASIA SYNDROME

Passarge, et al.[1] emphasized an autosomal recessive type of hypohidrotic ectodermal dysplasia and Gorlin, et al.[2] summarized the findings in 18 such pedigrees. The clinical features have not been distinguishable from the X-linked hypohidrotic ectodermal dysplasia, save for the fact that females are as severely affected as males. The natural history is similar to that of X-linked hypohidrotic ectodermal dysplasia, although they may have a greater problem with ozena (foul, purulent nasal discharge). The parents have been normal.

REFERENCES

1. Passarge, E., Nuzum, C. T., and Schubert, W. K.: Anhidrotic ectodermal dysplasia as autosomal recessive trait in an inbred kindred. Humangenetik, *3*:181, 1966.
2. Gorlin, R. J., Old, T., and Anderson, V. E.: Hypohidrotic ectodermal dysplasia in females. A critical analysis and argument for genetic heterogeneity. Z. Kinderheilkd, *108*:1, 1970.
3. Bartlett, R. C.,Eversole, L. R., and Adkins, R. S.: Autosomal recessive hypohidrotic ectodermal dysplasia: Dental manifestations. Oral Surg., *33*:736, 1972.





A, Female infant with presumed autosomal recessive type of hypohidrotic ectodermal dysplasia. *B*, Three affected sisters. (From Passarge, E., et al.: Humangenetik, *3*:181, 1966.)

RAPP-HODGKIN ECTODERMAL DYSPLASIA SYNDROME

(Hypohidrotic Ectodermal Dysplasia, Autosomal Dominant Type)

Hypohidrosis, Oral Clefts, Dysplastic Nails

Rapp and Hodgkin[1] reported three affected individuals in 1968 and Summitt and Hiatt[2] added one further case.

ABNORMALITIES

Growth. Variable growth deficiency.
Skin. Thin with hypohidrosis and sparse fine hair.
Nails. Small, narrow, dysplastic.
Teeth. Hypodontia with reduced, conical teeth.
Face. Low nasal bridge, narrow nose, maxillary hypoplasia.
Mouth. Small. Variable cleft of lip, palate, uvula.
Genitalia. Hypospadius.

NATURAL HISTORY. Liable to hyperthermia in early childhood. High frequency of purulent conjunctivitis and otitis media, the latter presumably related to palatal incompetence.

ETIOLOGY. Autosomal dominant, although X-linked dominant inheritance is not excluded. Sweat pores present, but markedly reduced in number on the palms.

REFERENCES

1. Rapp, R. S., and Hodgkin, W. E.: Anhidrotic ectodermal dysplasia: Autosomal dominant inheritance with palate and lip anomalies. J. Med. Genet., *5*:269, 1968.
2. Summitt, R. L., and Hiatt, R. L.: Hypohidrotic ectodermal dysplasia with multiple associated anomalies. Birth Defects, *7*(8):121, 1971.
3. Wannarachue, N., Hall, B. D., and Smith, D. W.: Ectodermal dysplasia and multiple defects (Rapp-Hodgkins type). J. Pediatr., *81*:1217, 1972.



Affected mother and children in Rapp and Hodgkin's[1] family. The mother is wearing a wig. Note the narrow nose, small mouth, and features of ectodermal dysplasia.

ROBINSON NAIL DYSTROPHY-DEAFNESS SYNDROME

(Robinson-Type Ectodermal Dysplasia)

Peg-Shaped Teeth, Nail Dystrophy, Deafness

Robinson, et al.[1] described five affected individuals in three generations of a family.

ABNORMALITIES. May have:
Teeth. Peg shape, partial anodontia.
Nails. Hypoplasia, dystrophy.
Hearing. Moderate sensorineural deafness.

OCCASIONAL ABNORMALITIES. Syndactyly, polydactyly. Note: some of the patients had elevated values for sweat electrolytes.

ETIOLOGY. Autosomal dominant.

REFERENCE

1. Robinson, G. C., Miller, J. R., and Bensimon, J. R.: Familial ectodermal dysplasia with sensorineural deafness and other anomalies. Pediatrics, *30*:797, 1962.

BJÖRNSTAD PILI TORTI-DEAFNESS SYNDROME

Björnstad[1] noted the association of twisted hair (pili torti) and sensorineural deafness in 1965, five of eight patients with the hair anomaly having deafness from an early age. Further cases have been recognized subsequently. The hair is grooved and flattened at irregular intervals, twisted, and breaks off with ease. The hearing loss, apparently due to cochlear defect, may be profound, and Björnstad noted a relationship between the degree of hair anomaly and the severity of deafness. The family data suggest an autosomal recessive mode of inheritance for this disorder.

REFERENCES

1. Björnstad, R.: Pili torti and sensori-neural loss of hearing. Proceedings, 17th Meeting, Northern Dermatological Society. Copenhagen, May, 1965.
2. Robinson, G. C., and Johnson, M. M.: Pili torti and sensorineural hearing loss. J. Pediat., *70*:621, 1967.

CLOUSTON SYNDROME

Nail Dystrophy, Dyskeratotic Palms and Soles, Hair Hypoplasia

Clouston in 1939 described 119 individuals in a French-Canadian family, and over 200 instances have been reported.

ABNORMALITIES. Most usual features:
Skin. Thick dyskeratotic palms and soles. Hyperpigmentation over knuckles, elbows, axillae, areolae, and pubic area.
Hair. Hypoplasia to alopecia (61 per cent).
Nails. Hypoplasia to aplasia, dysplasia.
Eyes. Strabismus.

OCCASIONAL ABNORMALITIES. Cataract, dull mentality, short stature.

ETIOLOGY. Autosomal dominant.

REFERENCES

1. Clouston, H. R.: The major forms of hereditary ectodermal dysplasia (with an autopsy and biopsies on the anhidrotic type). Can. Med. Assoc. J., *40*:1, 1939.
2. Wilkey, W. D., and Stevenson, G. H.: A family with inherited ectodermal dystrophy. Can. Med. Assoc. J., *53*:226, 1945.
3. Joachim, H.: Hereditary dystrophy of the hair and nails in six generations. Ann. Intern. Med., *10*:400, 1936.
4. Gold, R. J. M., and Scriver, C. R.: Properties of hair keratin in an autosomal dominant form of ectodermal dysplasia. Am. J. Hum. Genet., *24*:549, 1972.

TRICHO-DENTO-OSSEOUS SYNDROME

(TDO Syndrome)

Kinky Hair, Enamel Hypoplasia, Sclerotic Bone

Lichtenstein, et al.[1] recently defined this disorder in 107 individuals from one large kindred. Robinson, et al.[2] had previously described an autosomal dominant disorder with curly hair, enamel hypoplasia, +/− nail hypoplasia. Although it is not possible to be secure from the reported cases, the overall similarities are such as to suggest that they have the same disorder.

ABNORMALITIES

Hair. Kinky hair at birth.

Teeth. Small, widely spaced, pitted teeth with poor enamel, and increased pulp chamber size (taurodontism).

Facies. Frontal bossing, dolichocephaly, squarish jaw.

Bone. Mild to moderate increased bone density, most evident in lateral roentgenograms of skull.

Nails. Brittle with superficial peeling (about 50 per cent).

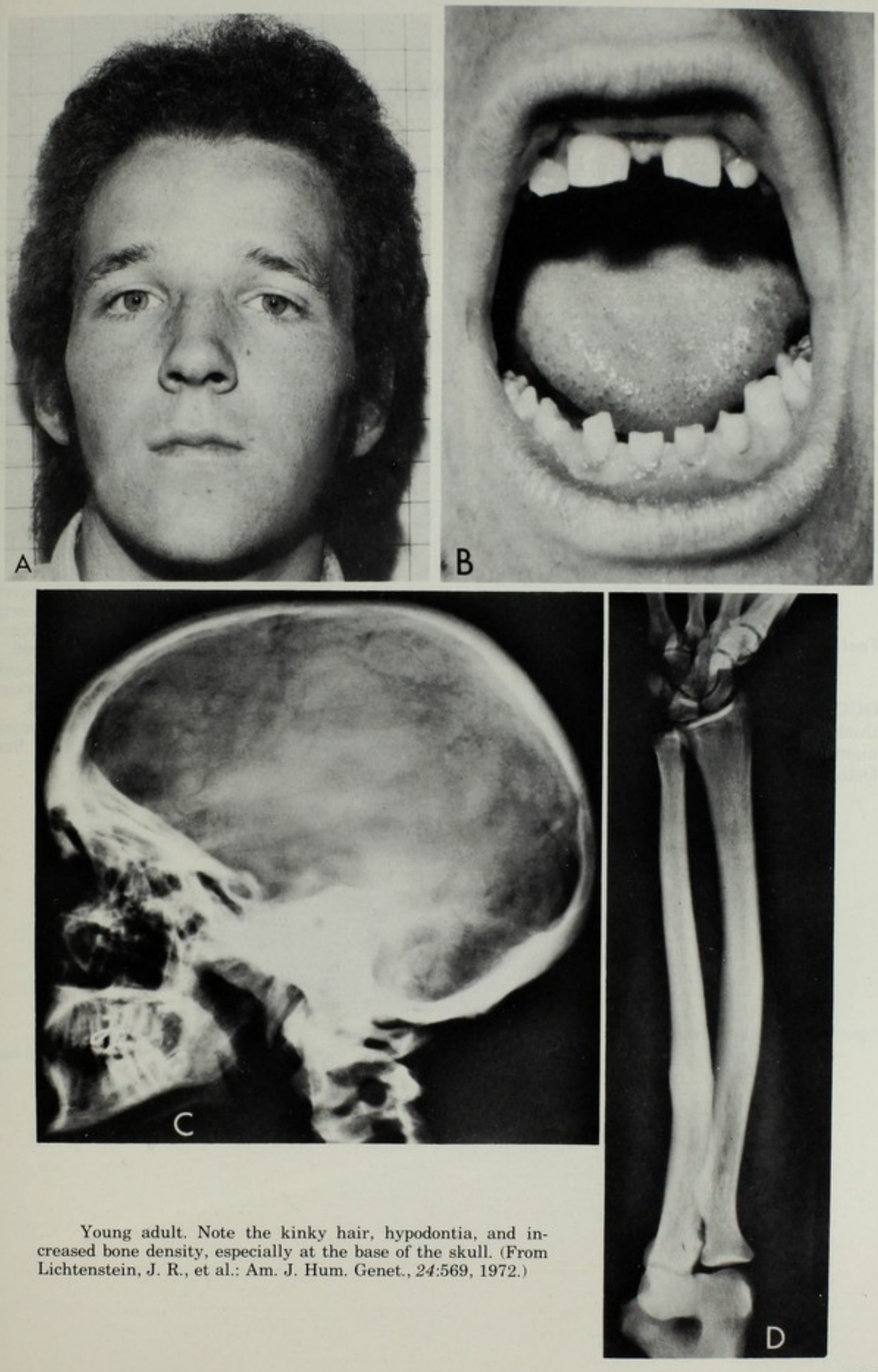
OCCASIONAL ABNORMALITIES. Partial craniosynostosis.

NATURAL HISTORY. The hair sometimes straightens with age. The teeth become eroded and discolored, are prone to periapical abscesses and are lost by the second to third decade. The sclerotic bone appears to be secondary to closely compacted lamellae and rarely associated with any clinical symptomatology.

ETIOLOGY. Autosomal dominant. Elevated serum acid phosphatase has been documented,[1] although the significance of the finding is unknown.

REFERENCES

1. Lichtenstein, J., Warson, R., Jorgenson, R., Dorst, J. P., and McKusick, V. A.: The Tricho-Dento-Osseous (TDO) syndrome. Am. J. Hum. Genet., *24*:569, 1972.
2. Robinson, G. C., Miller, J. R., and Worth, H. M.: Hereditary enamel hypoplasia. Its association with characteristic hair structure. Pediatrics, *37*:489, 1966.



Young adult. Note the kinky hair, hypodontia, and increased bone density, especially at the base of the skull. (From Lichtenstein, J. R., et al.: Am. J. Hum. Genet., *24*:569, 1972.)

PACHYONYCHIA CONGENITA SYNDROME

Thick Nails, Hyperkeratosis, Foot Blisters

Pachyonychia congenita is an ectodermal dysplasia described by Jadassohn and Lewandowsky[1] in which there is excessive keratin and occasionally extra teeth.

ABNORMALITIES

Nail. Progressive thickening of anterior half. The nails may eventually be hypoplastic or even absent.

Skin. Patchy to complete hyperkeratosis of palms and soles, callosities of feet which blister easily, and keratosis pilaris with tiny cutaneous horny excrescences.

Epidermal cysts filled with loose keratin on face, neck, and upper chest.

Mucous Membranes. Leukokeratosis of mouth and tongue, especially in positions of increased trauma.

Teeth. Erupted teeth at birth, lost by four to six months.

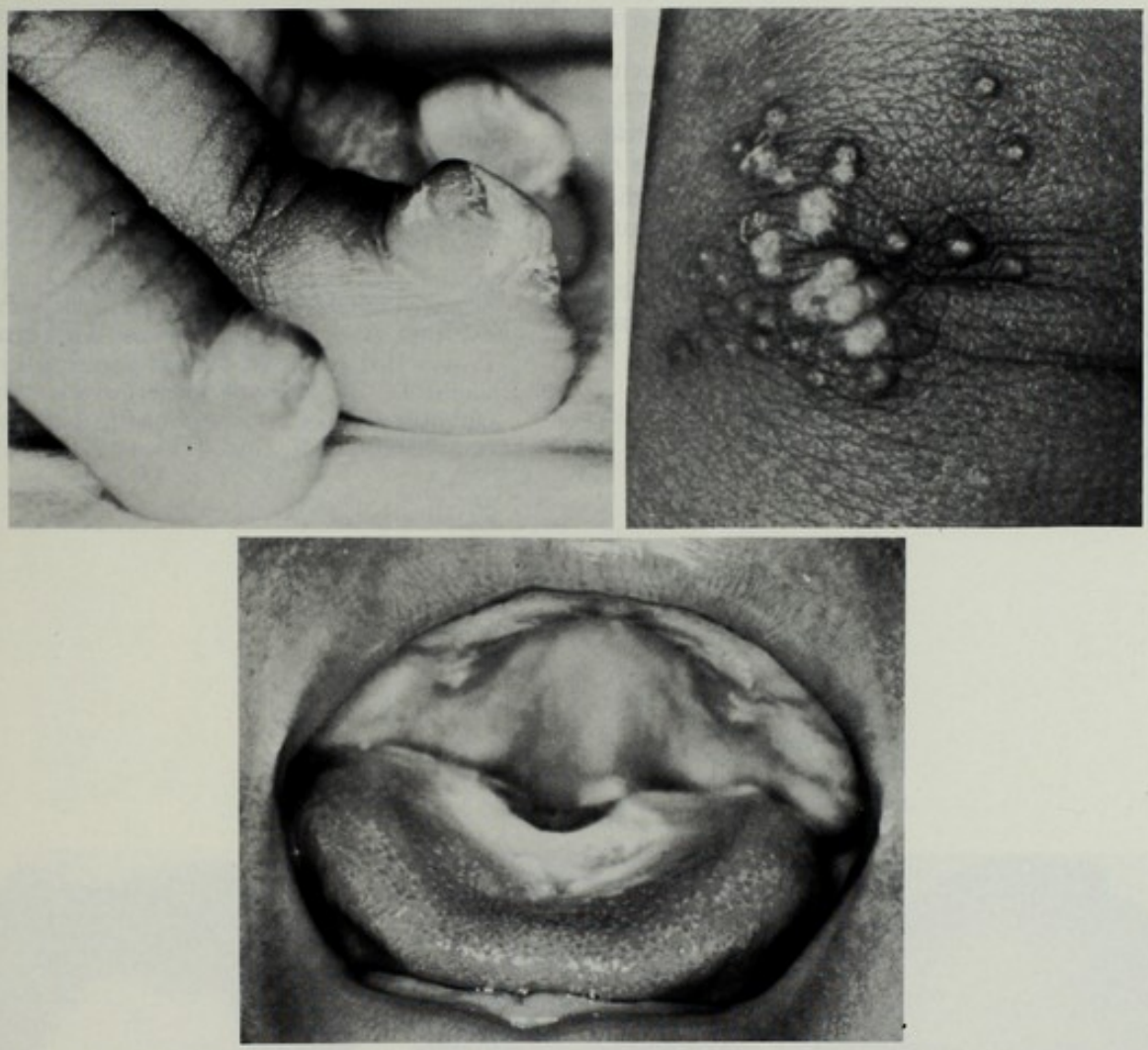
OCCASIONAL ABNORMALITIES. Corneal thickening, cataracts, thickening of tympanic membrane, hyperhidrosis. Hair dry and sparse. Osteomata, intestinal diverticuli.

NATURAL HISTORY. The complications are obvious. Usually the nails are grossly thickened by one year of age. Complete surgical removal of the nails is sometimes merited, although any matrix left behind will reform abnormal nails.

ETIOLOGY. Autosomal dominant, with wide variability in expression. Predominantly found in Slavs and Jews of Slavonic origin. The basic mechanism of the disease is unknown; however, vacuolization of the cytoplasm of nail matrix cells may be of significance.

REFERENCES

1. Jadassohn, J., and Lewandowsky, F.: Pachyonychia congenita, keratosis disseminata circumscripta (folliculosis): tylomata; leukokeratosis linguae. Ikonographia Dermatologica, Tab., *629*, 1906.
2. Soderquist, N. A., and Reed, W. B.: Pachyonychia congenita with epidermal cysts and other congenital dyskeratoses. Arch. Derm., *97*:31, 1968.
3. Young, L. L., and Lenox, J. A.: Pachyonychia congenita. A long term evaluation. Oral Surg., *36*:663, 1973.



Negro infant showing altered nails, cutaneous hyperkeratoses at knee, and leukokeratotic lesions on tongue and lateral palate.

PACHYDERMOPERIOSTOSIS SYNDROME

Thick Coarse Skin, Clubbing

This disorder was originally described by Friedreich[1] in 1868 and further clarified by Touraine, et al.[2] in 1935.

ABNORMALITIES[2, 3]

Skin. Development of coarse, thick, oily skin, especially over upper face and scalp, with secondary cutis verticis gyrata and sometimes ptosis of the eyelids. Hyperhidrosis of hands and feet, peripheral vascular stasis. Seborrheic hyperplasia with thick stratum corneum.

Limbs. Clubbing with periostosis, most pronounced at tendinous insertions. Joint and muscle discomfort.

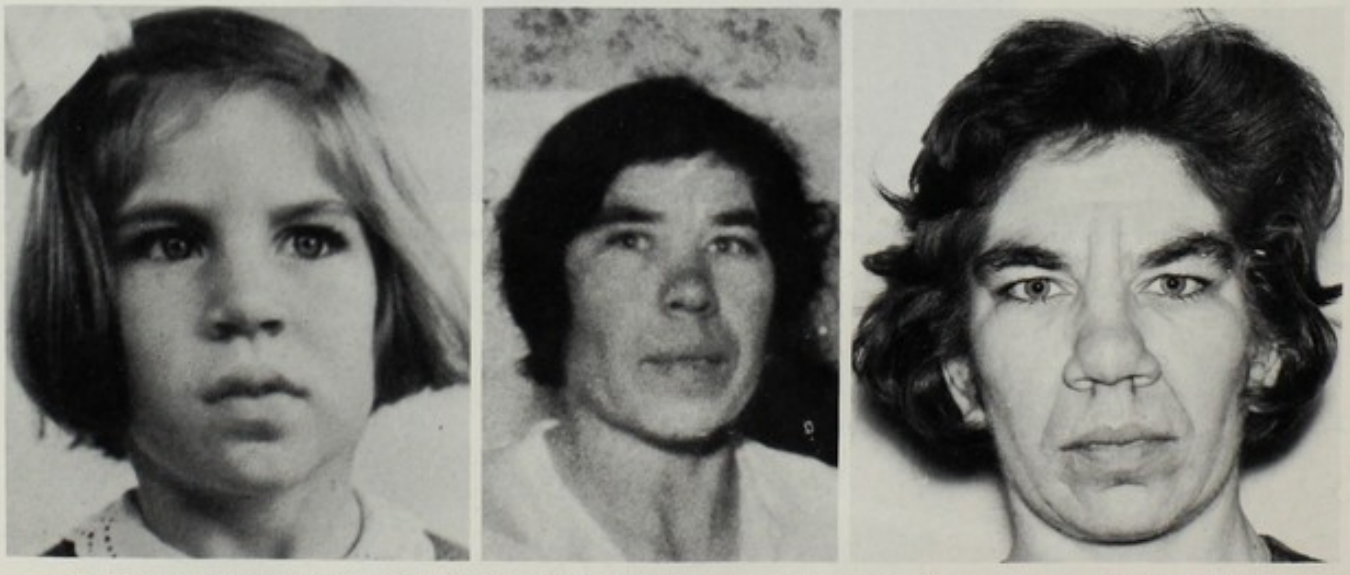
OCCASIONAL ABNORMALITIES. Papular mucinosis, large keloids.

NATURAL HISTORY. Earliest age of onset about three years, accentuation with adolescence and for a decade or so thereafter; more severe in males.

ETIOLOGY. Autosomal dominant with wide variance in expression.

REFERENCES

1. Friedreich, N.: Hyperostose des gesammten Skeletees. Virchow Arch. Path. Anat., *43*:83, 1868.
2. Touraine, A., Solente, G., and Golé, L.: Un syndrome ostéodermopathique: La pachydermie plicaturée avec pachypériostose des extrémités. Presse Med., *43*:1820, 1935.
3. Rimoin, D. L.: Pachydermoperiostosis (idiopathic clubbing and periostosis). Genetic and physiologic considerations. N. Eng. J. Med., *272*:923, 1965.



Child who showed evidence of the disorder at birth with an "acromegal" appearance. Although large as a child her adult height was 5 feet 6 inches. She had amenorrhea with a rudimentary uterus and small ovaries. The middle photo shows her at 30 years of age with progression in the thickening of skin and hirsutism. Her mother, shown to the right, was similarly but less severely affected. (From Ursing, B.: Acta Med. Scand., *188*:157, 1970.)

XERODERMA PIGMENTOSA SYNDROME

Undue Sunlight Sensitivity, Atrophic and Pigmentary Skin Changes, Actinic Skin Tumors

Xeroderma pigmentosa occurs in about one in 60,000 to 100,000 individuals.[1]

ABNORMALITIES[1]

Sunlight sensitivity with first exposure.

Progressive skin atrophy with irregular pigmentation, telangiectases, angiomata, keratoses, and development of basal cell and squamous carcinomata and melanomata.

May have aminoaciduria (overflow-type), defective teeth.

NATURAL HISTORY. Progressive disfigurement, tumors often by three to four years, most die of malignancy before 20 years.

ETIOLOGY. Autosomal recessive inheritance implicated with defect in repair of DNA after exposure to ultraviolet light. Can be tested in cultured fibroblasts from amniocentesis.[2]

REFERENCES

1. Rook, A., Wilkinson, D. S., and Ebling, F. J. G., eds.: Textbook of Dermatology. Oxford and Edinburgh, Blackwell Scientific Publications, 1968.
2. Kaback, M. M., Howell, R. R., Klein, E., and Burgess, G.: Xeroderma pigmentosum: a rapid sensitive method for prenatal diagnosis. Science, *174*:147, 1971.

FETAL ALCOHOL SYNDROME

Prenatal Onset Growth Deficiency, Microcephaly, Short Palpebral Fissures

In 1973, Jones, Smith, Ulleland, and Streissguth[1] delineated this disorder in eight unrelated children, all born to women who were severe chronic alcoholics prior to and during their pregnancy. Additional studies have confirmed the initial observations.[2, 3]

ABNORMALITIES: Variable features from the following:

Growth. Pre- and postnatal onset growth deficiency.

Performance. Average I.Q. of 63. Fine motor dysfunction manifested by weak grasp, poor eye-hand coordination, and/or tremulousness.

Craniofacial. Mild to moderate microcephaly, short palpebral fissures, maxillary hypoplasia.

Skeletal. Joint anomalies including abnormal position and/or function, altered palmar crease patterns.

Cardiac. Heart murmur, frequently disappearing by one year of age.

OCCASIONAL ABNORMALITIES. Ptosis, strabismus, cleft palate, unusual hirsutism in newborn period, capillary hemangioma, hypoplastic labia majora, pilonidal sinus.

NATURAL HISTORY. Birth length has been more severely affected than birth weight. Postnatal linear growth rate and rate of weight gain have averaged two thirds and one third of normal respectively, despite adequate caloric intake. The only autopsy done on a child known to have this disorder revealed severe structural alteration of the brain, including aberrations of neuronal migration and absence of the corpus callosum.

ETIOLOGY. Severe maternal alcoholism.

COMMENT. Evaluation of the charts of 23 offspring of a group of women ascertained purely by the history of chronic maternal alcoholism indicates a perinatal mortality of 17 per cent. Six of the 19 survivors were interpreted as having the Fetal Alcohol syndrome. The frequency of adverse outcome in the pregnancies of chronically alcoholic women is therefore of such magnitude that serious consideration should be given toward early termination of pregnancy in such women.

REFERENCES

1. Jones, K. L., Smith, D. W., Ulleland, C. N., and Streissguth, A. P.: Pattern of malformation in offspring of chronic alcoholic mothers. Lancet, *1*:1267, 1973.
2. Jones, K. L., and Smith, D. W.: Recognition of the Fetal Alcohol syndrome in early infancy. Lancet, *2*:999, 1973.
3. Jones, K. L., Smith, D. W., Streissguth, A. P., and Myrianthopoulous, N. C.: Outcome in offspring of chronic alcoholic women. Lancet, *1*:1076, 1974.



A



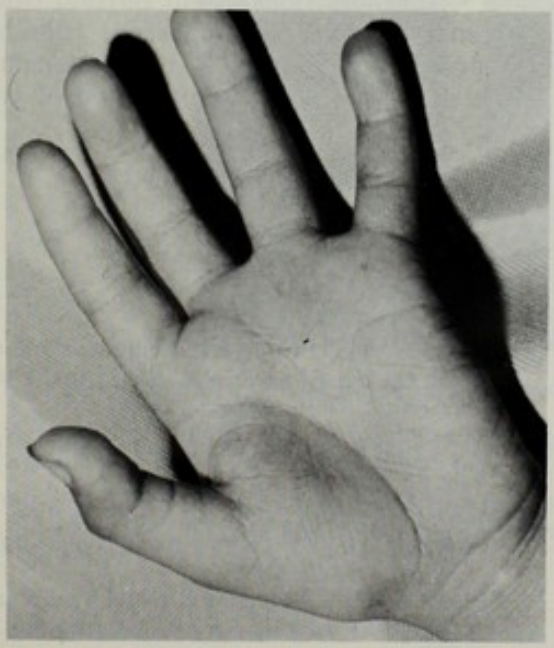
B



C



D



E

Affected children of chronic alcoholic women at birth *(A)*, one year *(B)*, two and one half years *(C)*, and three and three quarter years *(D)*. Note the short palpebral fissures for all children, strabismus *(B* and *D)*, ptosis of the eyelid *(D)*, and facial hirsutism in the newborn *(A)*. The hand shows mildly altered upper palmar crease patterning *(E)*. *(A* from Jones, K. L., and Smith, D. W.: Lancet, *2*:999, 1973; *B–E* from Jones, K. L., et al.: Lancet, *1*:1267, 1973.)

RUBELLA SYNDROME

Deafness, Cataract, Patent Ductus Arteriosus

Gregg[1] first called attention in 1941 to the permanent residua of fetal rubella acquired from the mother during the first trimester of gestation. Culture of the viral agent during the severe 1964 epidemic resulted in an appreciation of the "expanded rubella syndrome" as the consequence of widespread chronic disease.

ABNORMALITIES. Fetal death may occur. The following are tissues affected and consequent abnormalities noted in the 1964 epidemic.

The asterisks (*) indicate permanent residua.

Tissue	*Abnormality*
General hypoplasia	Growth deficiency
Central nervous system	*Mental deficiency, microcephaly
Cochlea	*Deafness
Lens	*Cataract
Other parts of eye	*Glaucoma, corneal opacity, chorioretinitis, microphthalmia, strabismus
Blood vessels	*Patent ductus arteriosus, peripheral pulmonic stenosis, fibromuscular proliferation with thickened intima of medium and large arteries
Myocardium	*Septal defects, myocardial disease

Early Infancy

Tissue	*Abnormalities*
Marrow elements	Thrombocytopenia, anemia
Reticuloendothelial	Hepatosplenomegaly
Liver	Obstructive jaundice
Bone	Osteolytic metaphyseal lesions
Lung	Interstitial pneumonia

OCCASIONAL ABNORMALITIES. Renal disease, hemolytic anemia, large anterior fontanel, late eruption of teeth, hypospadias, cryptorchidism, meningocele, dermatoglyphic alterations.

NATURAL HISTORY. The frequency of fetal infection from mothers having rubella during the first trimester is about 50 per cent. The risk still exists for rubella in the second trimester, especially for growth deficiency, deafness, mental deficiency, and peripheral pulmonic stenosis. Cultures for rubella virus in excretions were positive in 63 per cent of neonates with evidence of the Rubella syndrome; 31 per cent of cultures were still positive at five to seven months, 7 per cent at ten to 13 months, and none past the age of three years. However, rubella virus was recovered from a cataract removed from a three year old. Thus the disease is chronic and although the neonate has prenatal antibodies to the rubella agent, the intracellular rubella virus may persist for a long period of time.

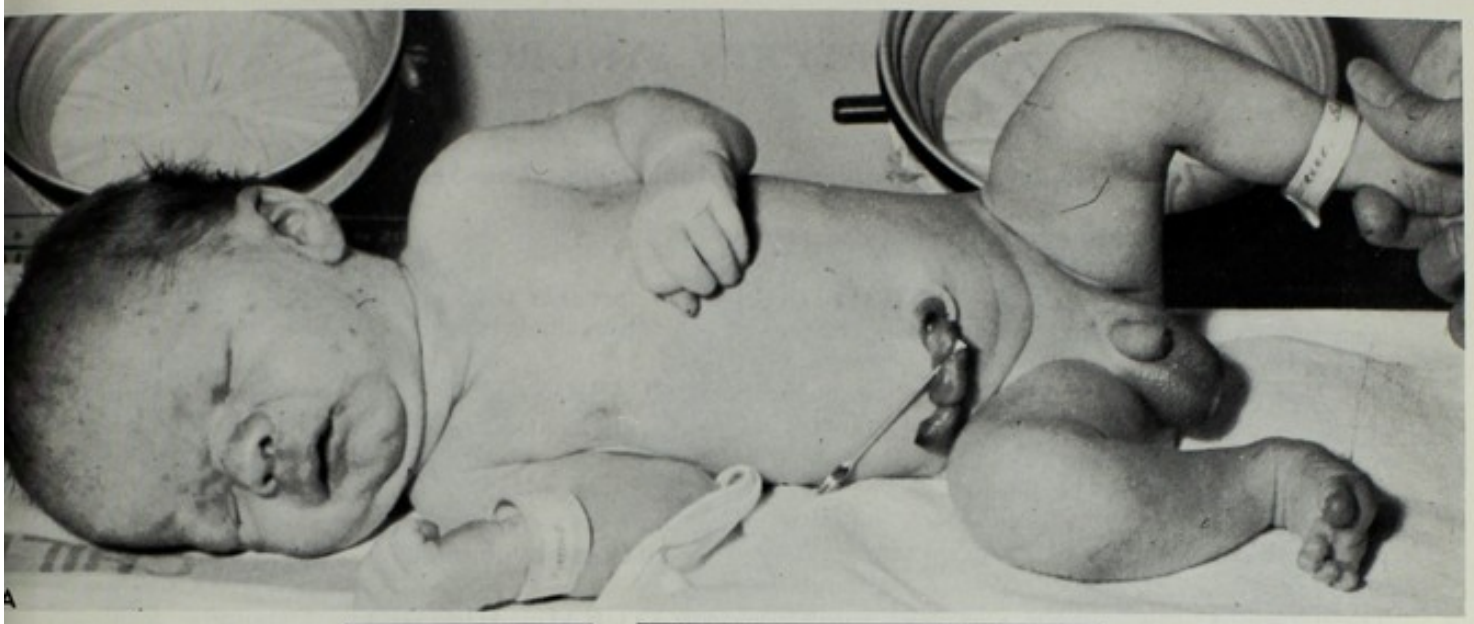
The frequence of residual defects, especially of mental deficiency (60 per cent I.Q. below 90 and 20 per cent below 70), was much higher in the 1964 epidemic than in those of the past, in which deafness was the most common residuum of fetal rubella (31 per cent).

Prevention of maternal rubella via widespread administration of attenuated rubella vaccine is thoroughly merited. Beyond this, the occurrence of validated maternal rubella during the first half of pregnancy merits serious consideration toward early termination of that pregnancy.

ETIOLOGY. Rubella virus.

REFERENCES

1. Gregg, N. McA.: Congenital cataract following German measles in the mother. Trans. Ophthalmol. Soc. Aust., *3*:35, 1941.
2. Cooper, L. Z., and Krugman, S.: Diagnosis and management: congenital rubella. Pediatrics, *37*:335, 1966.
3. Menser, M. A., Dods, L., and Harley, J. D.: A twenty-five-year follow-up of congenital rubella. Lancet, *2*:1347, 1967.
4. Hardy, J. B.: Clinical and development aspects of congenital rubella. Arch. Otolaryngol., *98*:230, 1973.







A, Newborn, clinically sick with lethargy, petechiae, and hepatosplenomegaly. (From Smith, D. W.: J. Pediatr., *70*:517, 1967.)

B, Osseous lesions in the femur of five day old baby. Note coarse trabecular pattern and subperiosteal rarefaction.

C, Three and three fourths year old with height age of two and three fourths years and mental deficiency. The patient has cataracts, chorioretinitis, hearing impairment, and cryptorchidism—all the apparent residua of congenital rubella.

AMINOPTERIN SYNDROME

Cranial Dysplasia, Broad Nasal Bridge, Low-Set Ears

The folic acid antagonist, aminopterin, has occasionally been utilized as an abortifacient during the first trimester of pregnancy. Thiersch[1] first noted abnormal morphogenesis in three abortuses and one full-term offspring of mothers who received aminopterin from four to nine weeks following the presumed time of conception. Subsequently other cases have been published, including toxicity secondary to methotrexate, the methyl derivative of aminopterin. The apparent dosage of the folic acid antagonist has ranged from 12 mg to 30 mg and it was taken between four and ten weeks of gestation. The similar pattern of malformation has consisted of cranial dysplasia, foot anomalies, and other less consistent defects.

ABNORMALITIES. Variable features, based on five cases.[2, 3]

Growth. Prenatal onset growth deficiency. Microcephaly.

Craniofacial. Severe hypoplasia of frontal bone, parietal bones, temporal or occipital bones, wide fontanels, and synostosis of lambdoid or coronal sutures. Upsweep of frontal scalp hair. Broad nasal bridge, shallow supraorbital ridges, prominent eyes, micrognathia, and cleft palate and low-set ears, with maxillary hypoplasia and epicanthal folds.

Limbs. Relative shortness, especially of forearm (mesomelia). Talipes equinovarus, hypodactyly and synostosis.

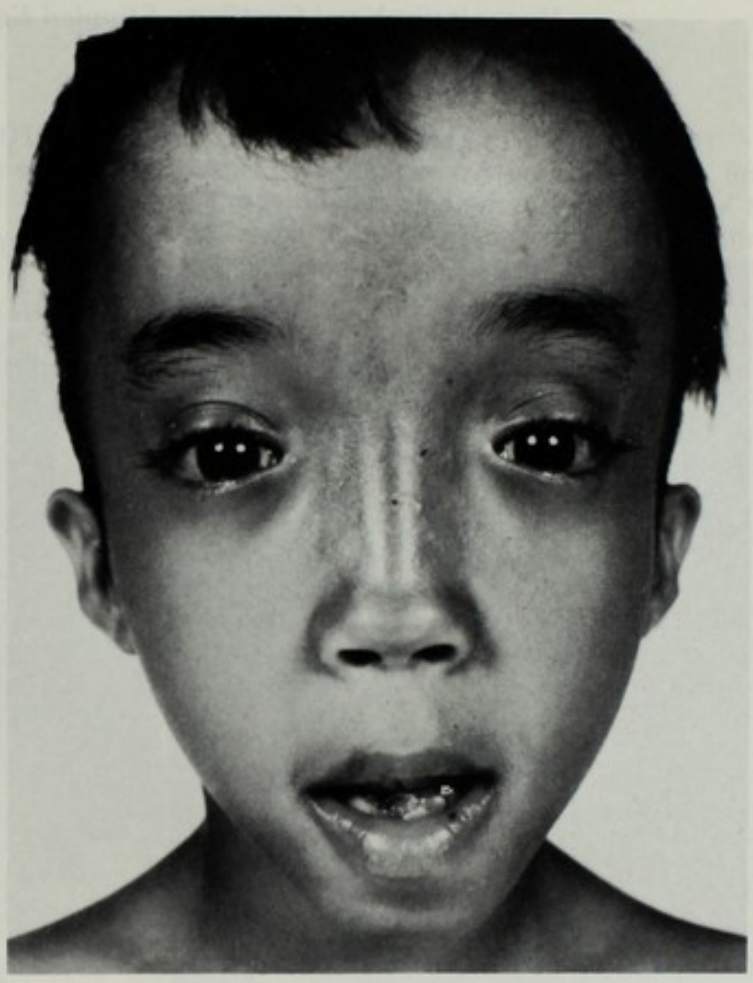
OCCASIONAL ABNORMALITIES. Cleft palate, dislocation of hip, retarded ossification of pubis and ischium, rib anomalies, short thumbs, partial syndactyly of third and fourth fingers, single crease on fifth finger, dextroposition of the heart, and hypotonia.

NATURAL HISTORY. Although fetal or early postnatal death has been the more usual outcome, at least two patients have survived beyond the first year of age. One was described as slow in growth but within normal limits in mental and motor performance[2] at 15 months of age. The other had slow growth and an I.Q. of 66 at four and one half years.[3]

REFERENCES

1. Thiersch, J. B.: Therapeutic abortions with a folic acid antagonist, 4-aminopteroylglutamic acid (4-amino P.G.A.) administered by the oral route. Am. J. Obstet. Gynec., *63*:1298, 1952.
2. Milunsky, A., Graef, J. W., and Gaynor, M. F., Jr.: Methotrexate induced congenital malformations with a review of the literature. J. Pediat., *72*:790, 1968.
3. Shaw, E. B., and Steinbach, H. L.: Aminopterin-induced fetal malformation. Am. J. Dis. Child., *115*:477, 1968.





Left, Affected newborn weighing 1.3 kg at 42 weeks' gestation. (From Warkany, J., et al.: Am. J. Dis. Child., *97*:274, 1959.)

Right, Affected boy. (Courtesy of Dr. Noreen L. Rudd, Toronto.)

FETAL WARFARIN SYNDROME

(Coumadin Syndrome, Warfarin Syndrome)

Hypoplastic Nasal Cartilage, Stippled Epiphyses, Warfarin Exposure

Di Saia[1] first reported this disorder in 1966 and the total number of recognized instances is at least five.[2, 3] The mothers have had prosthetic mitral valves and for this reason have received warfarin (Coumarin) as an anticoagulant.

ABNORMALITIES. Variable features from the following:

Performance. Developmental and mental deficiency, hypotonia, seizures, optic atrophy.

Facies. Hypoplastic nose with low nasal bridge; variable upper airway obstruction.

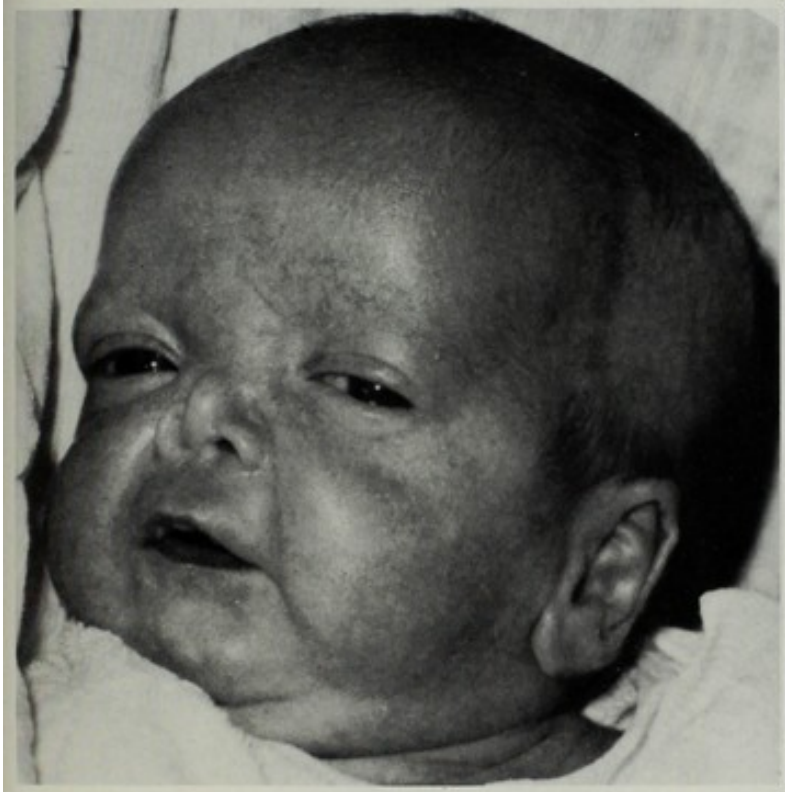
Skeletal. Stippled mineralization in epiphyses, vertebrae, nasal cartilage.

NATURAL HISTORY. The babies tend to feed poorly and show variable evidence of mental deficiency.

ETIOLOGY. Warfarin. Pathogenesis unknown.

REFERENCES

1. Di Saia, P. J.: Pregnancy and delivery of a patient with a Starr-Edwards mitral valve prosthesis. Report of a case. Obstet. Gynecol., *28*:469, 1966.
2. Kerber, I. J., Warr, O. S., and Richardson, C.: Pregnancy in a patient with a prosthetic mitral valve associated with the fetal anomaly attributed to warfarin sodium, J.A.M.A., *203*:223, 1968.
3. Holmes, L. B., et al.: Mental Retardation – An Atlas of Diseases with Associated Physical Abnormalities. New York, The Macmillan Co., 1972, p. 136.
4. Shaul, W. L., Emery, H., and Hall, J. G.: Chondrodysplasia punctata and maternal Warfarin use during pregnancy. Am. J. Dis. Child., *129*:360, 1975.





Patient at five days of age. Note hypoplastic nose with low nasal bridge and broad, flat face. Roentgenogram at one day of age showing stippling along the vertebral column, in the sacral area and proximal femurs. Stippling was also noted in the cervical vertebrae, acromion process, and tarsal bones. (From Shaul, W. L., Emery, H., and Hall, J. G.: Am. J. Dis. Child., *129*:360, 1975.

FETAL TRIMETHADIONE SYNDROME

(Tridione Syndrome)

In 1970 German, et al.[1] reported significant abnormalities among the offspring of four women treated with trimethadione or paramethadione. More than 20 affected offspring are now known.

ABNORMALITIES. Varying features from the following:

Performance. Mental deficiency, speech disorders.

Growth. Prenatal onset growth deficiency.

Craniofacial. Mild brachycephaly. Mild midface hypoplasia, short upturned nose with broad and low nasal bridge, prominent forehead, mild synophrys with unusual upslant to eyebrows. Strabismus, ptosis, epicanthic folds. Cleft lip and palate, high arched palate, micrognathia. Poorly developed rectangular or cupped and overlapping helix.

Cardiovascular. Septal defects, tetralogy of Fallot.

Genitourinary. Ambiguous genitalia, hypospadius, clitoral hypertrophy.

Limb. Simian crease.

OCCASIONAL ABNORMALITIES. Facial hemangiomas, web neck, scoliosis, transposition of the great vessels, hypoplastic heart, pyloric stenosis, renal anomalies, umbilical and inguinal hernias, hearing and visual deficits, and dislocated hip.

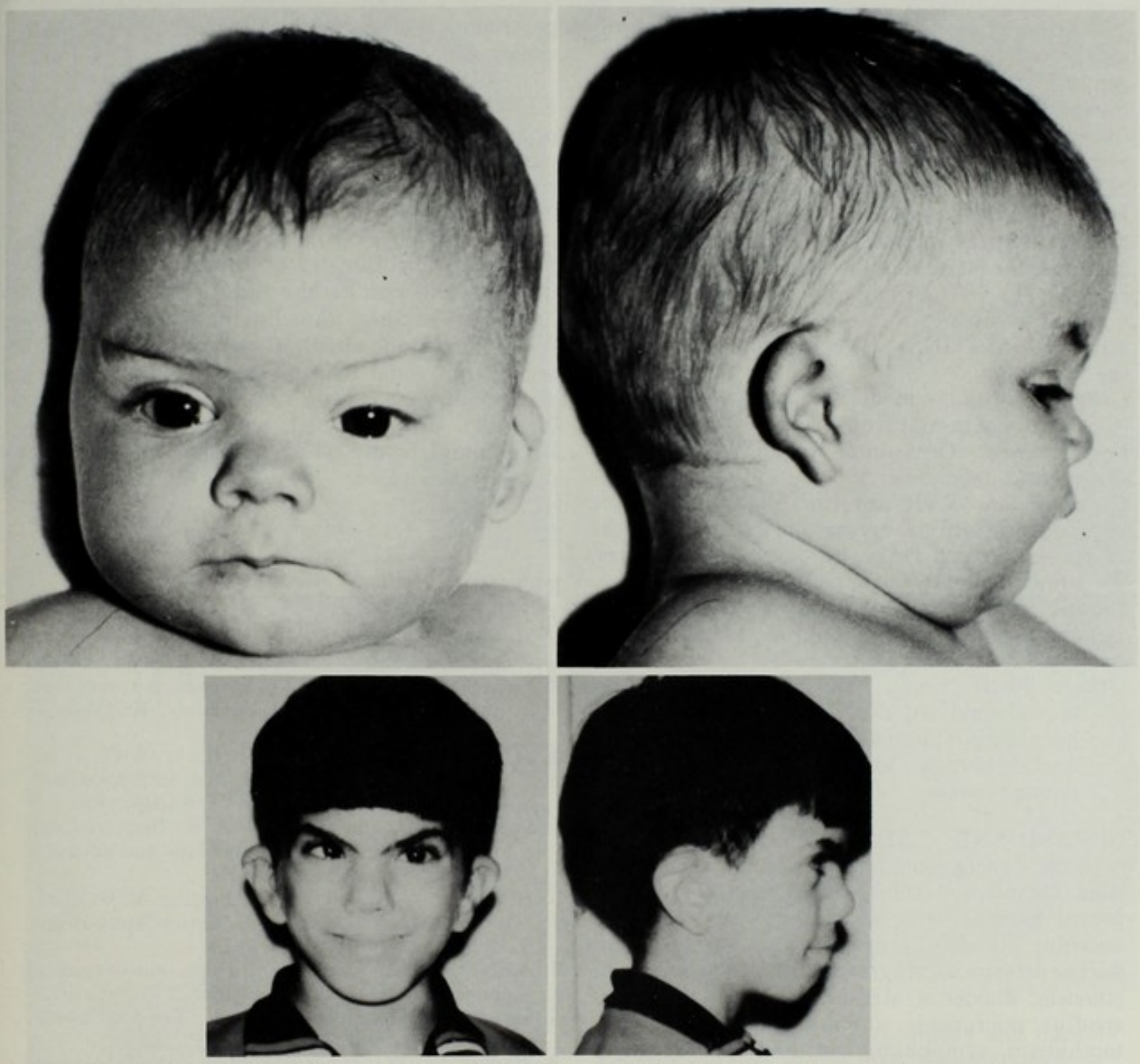
NATURAL HISTORY. Mental deficiency and serious cardiac defects give many cases a poor prognosis.

ETIOLOGY. Both trimethadione and its close congener paramethadione have been associated with a similar constellation of defects. More than two thirds of pregnancies in women known to be taking these drugs have resulted in children with significant abnormalities. The frequency of spontaneous abortion may also be increased.

COMMENT. The frequency and severity of defects associated with maternal use of these drugs during pregnancy is high enough to warrant consideration of early elective termination of pregnancy.

REFERENCES

1. German, J., Lowal, A., and Ehlers, K. H.: Trimethadione and human teratogenesis. Teratology, *3*:349, 1970.
2. Zackai, E., Mellman, M. J., Neiderer, B., and Hanson, J. W.: The fetal trimethadione syndrome. J. Pediatr., *87*:280, 1975.



Above, Five month old with tetralogy of Fallot whose mother took trimethadione throughout pregnancy. Note ear malformation, hypoplastic midface, and unusual eyebrow configuration. (Courtesy of J. Hanson, University of Washington.)

Below, Ten year old with speech delay whose mother took trimethadione during pregnancy. Note ear malformation, unusual slant to eyebrows, and strabismus. (Courtesy of E. Zackai, Philadelphia Children's Hospital.)

FETAL HYDANTOIN SYNDROME

(Dilantin Syndrome, Hydantoin Syndrome)

Although data suggesting the possible teratogenic effects of anticonvulsants was first presented by Meadow[1] in 1968, convincing epidemiologic evidence of the association between hydantoins and congenital abnormalities awaited the studies of Fedrick[2] and Monson, et al.[3] Further studies by Speidel and Meadow[4] and Hill, et al.[5] have revealed a pattern of malformation which may include digit and nail hypoplasia, unusual facies, and growth and mental deficiency.

ABNORMALITIES. Varying combinations of the following:

Growth. Mild to moderate growth deficiency, usually of prenatal onset.

Performance. Occasional borderline to mild mental deficiency.

Craniofacial. Wide anterior fontanel, metopic ridging, ocular hypertelorism, broad depressed nasal ridge, low-set abnormal ears, broad alveolar ridge, cleft lip and palate.

Limbs. Hypoplasia of distal phalanges with small nails, digital thumb, dislocation of hip.

Other. Short neck, rib anomalies, widely spaced small nipples, umbilical and inguinal hernias, pilonidal sinus, coarse profuse scalp hair, hirsutism, low-set hair line, abnormal palmar crease.

OCCASIONAL ABNORMALITIES. Microcephaly, brachycephaly, positional foot deformities, strabismus, coloboma, ptosis, slanted palpebral fissures, web neck, pulmonary or aortic valvular stenosis, coarctation of aorta, patent ductus arteriosus, single umbilical artery, pyloric stenosis, duodenal atresia, anal atresia, hypospadius, micropenis, ambiguous genitalia, cryptorchidism, symphalangism, and syndactyly.

NATURAL HISTORY. Some improvement may be seen in the growth of nails and distal phalanges, and in the reduction of gingival hypertrophy; however, growth and mental deficiency appear to be permanent when they occur.

ETIOLOGY. Although only the effects of diphenylhydantoin (Dilantin) have been sufficiently studied to warrant definite conclusions, closely related compounds should be regarded as potentially adverse to the fetus. Furthermore, there is evidence[2, 4] that combinations of hydantoins plus barbiturates or their congeners may increase the risk to the fetus. The risk of the hydantoin-exposed fetus having the fetal hydantoin syndrome is about 10 per cent, and the risk for having some features of the disorder is an additional 33 per cent.[8] No dose response curve has been demonstrated, nor has a "safe" dose been found below which there is no increased teratogenic risk.

REFERENCES

1. Meadow, S. R.: Anticonvulsant drugs and congenital abnormalities. Lancet, *2*:1296, 1968.
2. Fedrick, J.: Epilepsy and pregnancy: A report from the Oxford Record Linkage Study. Br. Med. J., *2*:442, 1973.
3. Monson, R. R., Rosenberg, L., Harty, S. C., et al.: Diphenylhydantoin and selected congenital malformations. N. Engl. J. Med., *289*:1049, 1973.
4. Speidel, B. D., and Meadow, S. R.: Maternal epilepsy and abnormalities of the fetus and newborn. Lancet, *2*:839, 1972.
5. Hill, R. M. Vermaud, W. M., Horning, M. G., et al.: Infants exposed in utero to antiepileptic drugs. Am. J. Dis. Child., *127*:645, 1974.
6. Aase, J. M.: Anticonvulsant drugs and congenital abnormalities. Am. J. Dis. Child., *127*:758, 1970.
7. Hanson, J. W., and Smith, D. W.: The fetal hydantoin syndrome. J. Pediatr., *87*:285, 1975.
8. Hanson, J. W., Myrianthopoulos, N. C., Harvey, M. A. S., and Smith, D. W.: Risks to the offspring of women treated with hydantoin anticonvulsant, with emphasis on the fetal hydantoin syndrome. J. Pediatr., in press.



Fifteen month old with growth and mental deficiency whose mother took diphenylhydantoin and phenobarbital throughout pregnancy. Note the hypoplastic nails and phalanges, mild ptosis, relatively low and broad nasal bridge, and coarse hair. (Courtesy of J. Hanson, University of Washington.)

COFFIN-SIRIS SYNDROME

Hypoplastic to Absent Fifth Finger and Toenails, Coarse Facies

Coffin and Siris[1] reported three patients with this disorder in 1970 and Weiswasser, et al.[2] reported an additional case in 1973. Also, several of the patients described by Senior[3] might represent examples of this syndrome.

ABNORMALITIES[1, 2]

Growth. Prenatal onset of mild to moderate growth deficiency.

Performance. Mental deficiency, moderate to severe hypotonia.

Craniofacial. Mild microcephaly. Coarse facies with full lips.

Limbs. Hypoplastic to absent fifth finger and toenails with lesser hypoplasia in other digits. Lax joints with radial dislocation at elbow. Coxa valga. Small patellae.

Hair. General hirsutism with tendency to sparse scalp hair.

OCCASIONAL ABNORMALITIES. Ptosis of eyelids, hypotelorism, preauricular skin tag, hemangioma, cryptorchidism, hernias, short sternum, cardiac defect, short forearm, vertebral anomalies, cleft palate, Dandy-Walker anomaly of brain.

NATURAL HISTORY. Feeding problems and recurrent upper and lower respiratory infection are frequent during early life.

ETIOLOGY. Unknown; sporadic occurrence. Similar nail hypoplasia has been noted in some babies born of women who received dilantin and phenobarbital therapy during preganacy.

REFERENCES

1. Coffin, G. S., and Siris, E.: Mental retardation with absent fifth fingernail and terminal phalanx. Am. J. Dis. Child, *119*:433, 1970.
2. Weiswasser, W. H., Hall, B. D., Delavan, G. W., and Smith, D. W.: Coffin-Siris syndrome: Two new cases. Am. J. Dis. Child., *125*:838, 1973.
3. Senior, B.: Impaired growth and onychodysplasia. Short children with tiny toenails. Am. J. Dis. Child., *122*:7, 1971.



The three original patients. (From Coffin, G. S., and Siris, E.: Am. J. Dis. Child., *119*:433, 1970.)

LERI PLEONOSTEOSIS SYNDROME

Broad Thumb, Joint Limitation, Upward Slant to Palpebral Fissures

Leri[1] described this disease in 1922. Though many instances have been reported in the French literature, it has received little recognition in the English literature.

ABNORMALITIES[2, 3]

Joints and Fibrous Tissues. Postnatal onset of thickened joint contractures, especially hands.

Thick palms and soles.

Skeletal. Broad thumbs and great toes with short "spade-like" hand.

Posterior neural arches increased in height.

Large paranasal sinuses.

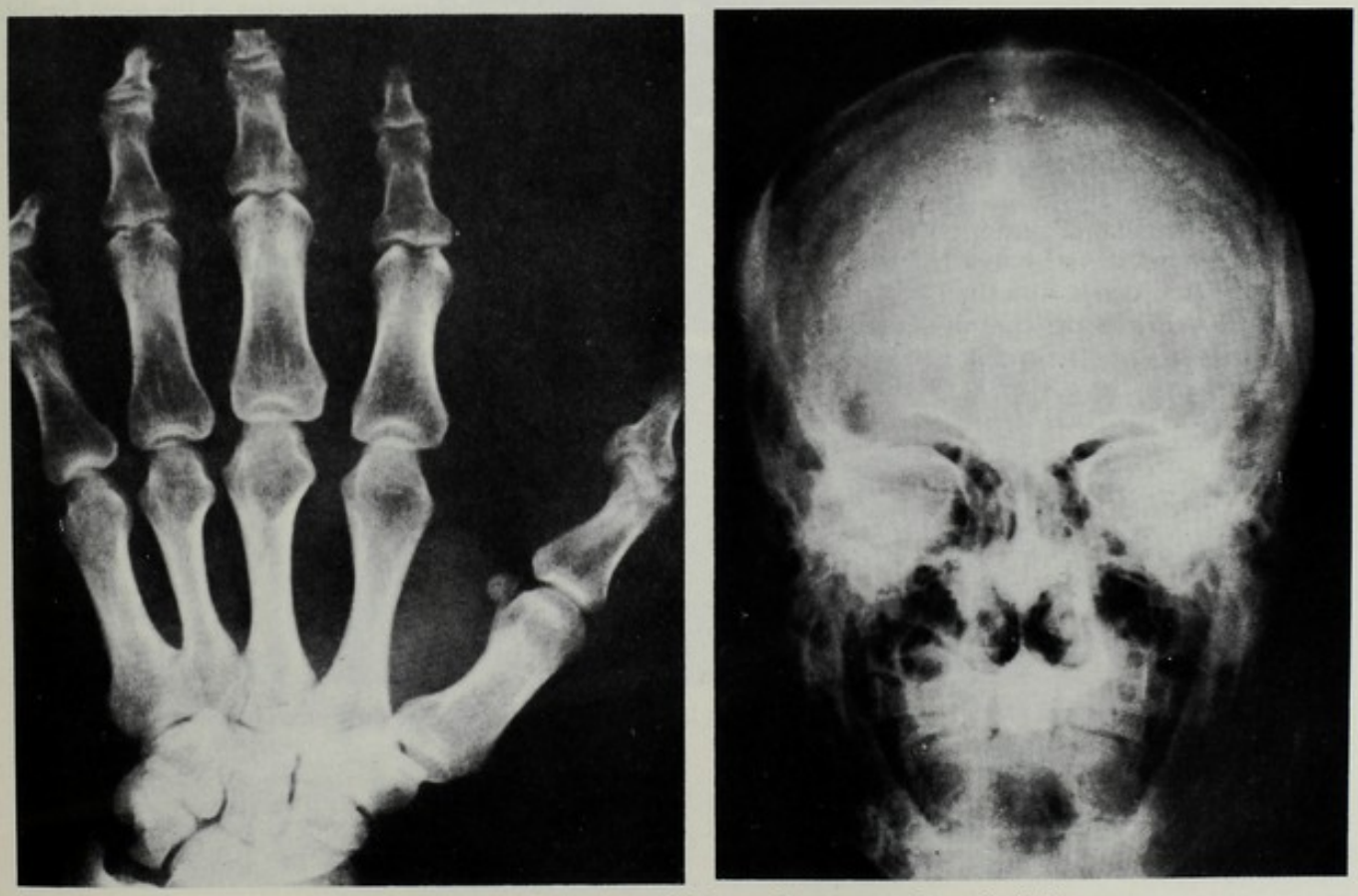
Facies. Mild upward slant to palpebral fissures.

NATURAL HISTORY. The joint limitations apparently begin in childhood and can progress into adult life.

ETIOLOGY. Autosomal dominant with full penetrance and varying expressivity.

REFERENCES

1. Leri, A.: Une maladie congénitale et héréditaire de l'ossification: la pléonostéose familiale. Presse Med., *30*:13, 1922.
2. Rukavina, J. G., Falls, H. F., Holt, J. F., and Block, W. D.: Leri's pleonosteosis. A study of a family with a review of the literature. J. Bone Joint Surg., *41-A*:397, 1959.
3. McKusick, V.: Hereditable disorders of Connective Tissue, 3rd ed. St. Louis, C. V. Mosby Co., 1966, p. 419.



Left, Short and relatively broad and deformed metacarpals and phalanges.
Right, Large paranasal sinuses.
(From Rukavina, J. G., et al.: J. Bone Joint Surg. [Am.], *41A*:397, 1959.)

LAURENCE-MOON-BIEDL SYNDROME

Retinal Pigmentation, Obesity, Polydactyly

The variable manifestations of this syndrome were initially described by Laurence and Moon in 1865,[1] and the clinical phenotype was further delineated and popularized by Bardet and Biedl in the 1920's. Subsequently more than 300 cases have been reported.

PRINCIPAL ABNORMALITIES

Obesity	83%
Mental deficiency	80%
Polydactyly, syndactyly, or both	75%
Retinitis pigmentosa	68%
Genital hypoplasia, hypogonadism, or both	60%

OTHER DEFECTS. Renal defect (including a chronic glomerulonephritis type of lesion) and nerve deafness are features observed in this syndrome; however, their incidence is unknown. Occasional defects include nystagmus, strabismus, diabetes insipidus, clinodactyly of the fifth finger. Moderate shortness of stature may also be a feature.

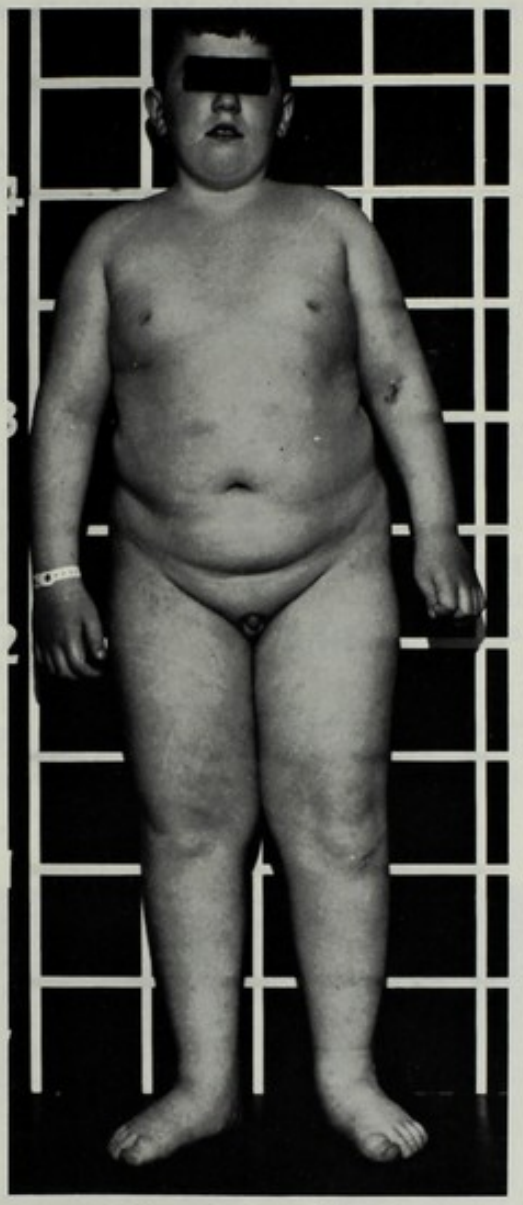
NATURAL HISTORY. The natural history of this condition is poorly outlined in the literature. The mental deficiency is usually mild to moderate, and the retinal degeneration generally results in problems of night vision during childhood, even by three years of age. Only about 15 per cent of patients show an atypical retinal pigmentation by five to ten years of age. Central vision is lost and then peripheral vision. By age 20 years 73 per cent of patients are blind. There may also be neurological evidence of spinocerebellar degeneration or cranial nerve palsy. Obesity is usually present from early infancy. Hypogonadism has been described as primary germinal hypoplasia and also as hypogonadotropic in type. It is important to appreciate that some of the patients undergo a spontaneous adolescent change.

ETIOLOGY. Autosomal recessive.

COMMENT. The extent of abnormality may vary considerably between affected siblings, and it may be impossible to make the diagnosis of Laurence-Moon-Biedl syndrome in an isolated case demonstrating only a part of the syndrome, especially only mental retardation, obesity, and genital hypoplasia.

REFERENCES

1. Laurence, J. Z., and Moon, R. C.: Four cases of "retinitis pigmentosa," occurring in the same family, and accompanied by general imperfections of development. Ophthalmol. Rev., *2*:32, 1865.
2. Bell, J.: The Laurence-Moon syndrome. *In* The Treasury of Human Inheritance, Vol. 5, Part 3, edited by L. S. Penrose. London, Cambridge University Press, 1958.
3. Blumel, J., and Kniker, W. T.: Laurence-Moon-Bardet-Biedl syndrome. Tex. Rep. Biol. Med., *17*:391, 1959.
4. Bauman, M. L., and Hogan, G. R.: Laurence-Moon-Biedl Syndrome. Am. J. Dis. Child., *126*:119, 1973.







Ten year old male with retinal pigmentation and renal insufficiency. Obesity from birth. I.Q., 52.

RIEGER SYNDROME

Iris Dysplasia, Hypodontia, Myotonic Dystrophy

Rieger[1] described this association of anomalies in 1935.

ABNORMALITIES

Eye. Dysplasia of iris including hypoplasia, mesenchymal tissue filling in the angle of the anterior chamber, and aberrant synechiae of iris.

Teeth. Hypodontia, partial anodontia, or both.

Neurologic. Variable myotonic dystrophy.

OCCASIONAL ABNORMALITIES. Eye: glaucoma, microcornea, corneal opacity, ectopia lentis, aniridia, optic atrophy. Mental deficiency.

ETIOLOGY. Autosomal dominant with rather wide variance in expression. It is difficult to know whether all cases described as Rieger's syndrome are the same etiologic entity.

COMMENT. Iris dysplasia of the type noted by Rieger has been reported as a dominantly inherited anomaly without any other defect.[3]

REFERENCES

1. Rieger, H.: Beiträge zur Kenntnis seltener Missbildungen der Iris. Arch. Ophthalmol., *133*:602, 1935.
2. Busch, G., Weiskopf, J., and Busch, K.-T.: Dysgenesis mesodermalis et ectodermalis Rieger oder Rieger'sche Krankheit. Klin. Monatsbl. Augenheilkhd., *136*:513, 1960.
3. Pearce, W. G., and Kerr, C. B.: Inherited variation in Rieger's malformation. Br. J. Ophthalmol., *49*:530, 1965.



Father and daughter with iris dysplasia. The daughter has two irregular pupils on the right and three on the left. The father has severe loss of vision with corneal opacification secondary to glaucoma. Both have hypodontia, maxillary hypoplasia with malocclusion, and a short philtrum. In addition, the daughter had sagittal craniosynostosis.

MOORE-FEDERMAN SYNDROME

(Familial Dwarfism and Stiff Joints)

Short Stature of Childhood Onset, Stiff Joints, Hyperopia

Moore and Federman[1] described this pattern of altered connective tissue development in six individuals in three generations of one family in 1965. They recognized the similarity of their patients to those with the Leri syndrome of "familial pleonosteosis";[2] however, it is not presently possible to be certain whether they represent the same entity.

ABNORMALITIES. Based on six cases.[1]

Growth. Short stature, onset in childhood.

Joints. Limited motility at elbow, knee, wrist, and fingers, especially at thickened distal phalangeal joints.

Skin. Taut and somewhat thickened over joints.

Eye. Hyperopia (five).

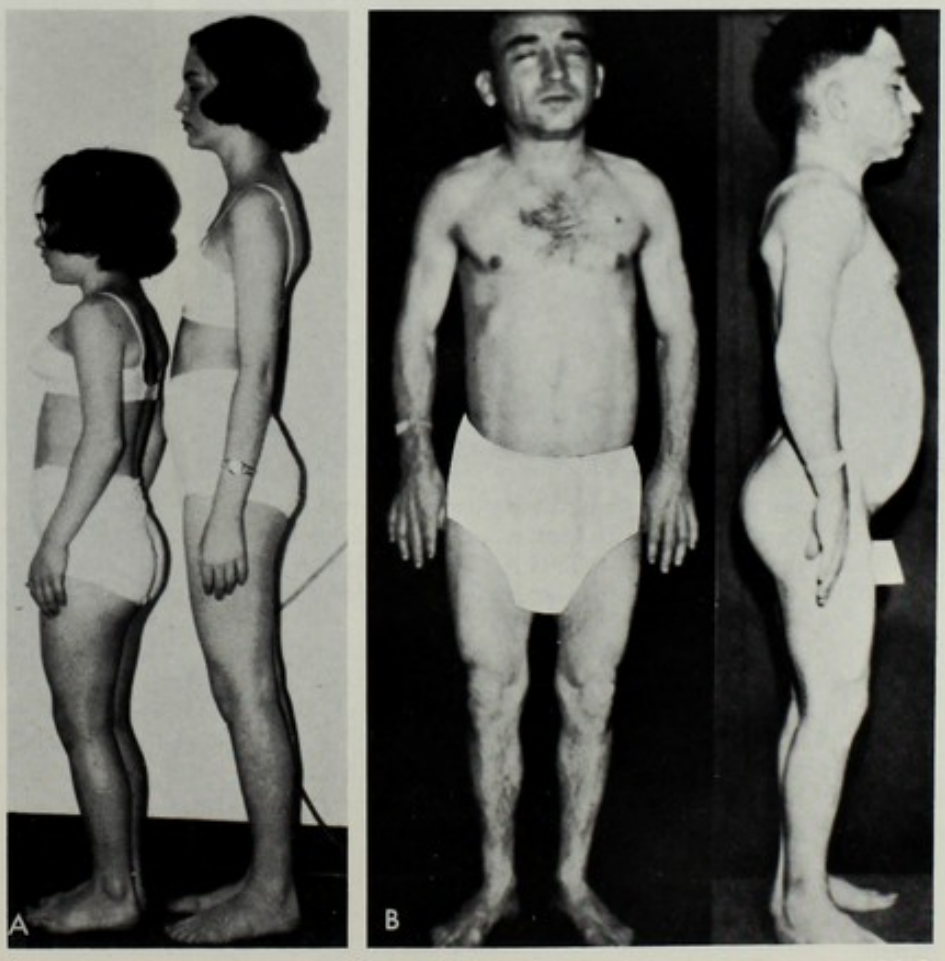
Other. Asthma (four), hoarse voice (three), hepatomegaly (three).

NATURAL HISTORY. Apparently normal at birth; slow growth and joint stiffness noted by three to five years, with gradual progression and eventual inability to clench the hand completely. The span tends to be less than height; adult height varied from 54 to 57 inches. Other than slightly widened phalangeal metaphyses and diminished height of vertebrae, no alteration in bony form was noted. Glaucoma, cataract, and retinal detachment developed in one adult and may represent a serious threat to vision in later life. Asthma, especially in association with respiratory infections, was a frequent feature in later childhood (after five years).

ETIOLOGY. Autosomal dominant.

REFERENCES

1. Moore, W. T., and Federman, D. D.: Familial dwarfism and "stiff joints." Report of a kindred. Arch. Intern. Med., *115*:398, 1965.
2. Leri, A.: Une maladie congénitale et héréditaire de l'ossification: la pléonostéose familiale. Presse Med., *30*:13, 1922.



A, Sixteen year old girl with normal girl of similar age.

B, Father of affected girl in *A*, showing short stature and stiff joints. (From Moore, W. T., and Federman, D. D.: Arch Int. Med., *115*:398, 1965.)

CEREBRO-COSTO-MANDIBULAR SYNDROME

Rib-Gap Defect with Small Thorax, Severe Micrognathia

Initially described by Smith, et al.[1] in 1966, this disorder was further established by Doyle[2] and by McNicholl, et al.,[3] who reported three affected siblings.

ABNORMALITIES

Growth. Prental onset growth deficiency. Birth weight 2.5 to 2.9 kg.

Facies. Severe micrognathia with glossoptosis and short to cleft soft palate.

Thorax. Bell-shaped small thorax with gaps between posterior ossified rib and anterior cartilagenous rib, especially fourth to tenth ribs. Anomalous rib insertion to vertebrae.

Other. Inconsistent observations of redundant skin, abnormal tracheal cartilagenous rings, vertebral anomalies, and elbow hypoplasia.

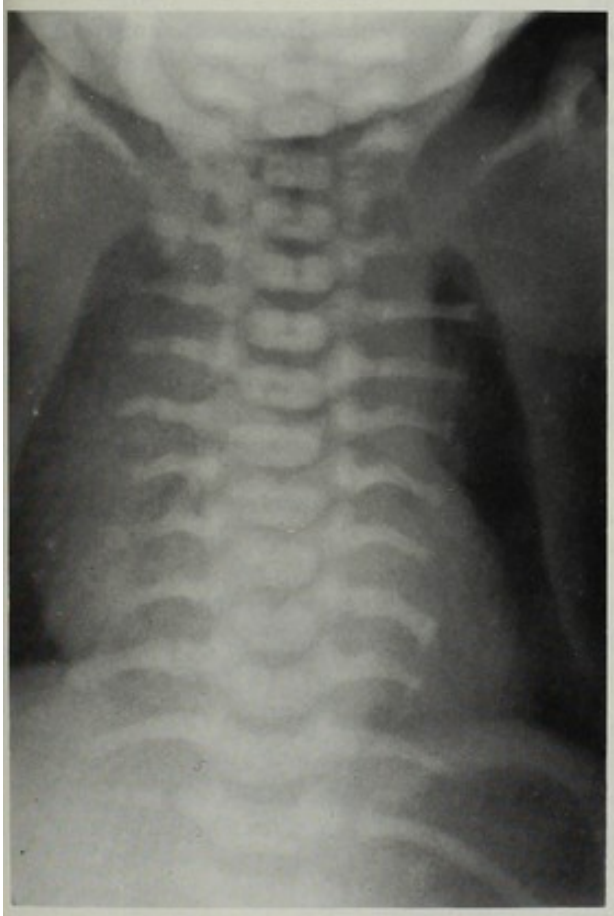
NATURAL HISTORY. Generally an early lethal course because of respiratory insufficiency; the only survivor was tube-fed during the first year during which time there were multiple respiratory infections and diarrhea. At six years of age this child had a mental age of one year and height age of three years. Considering the natural history, it is questionable whether any medical interference should be utilized when this disorder is diagnosed early in life.

ETIOLOGY. Autosomal recessive inheritance is implied by the occurrence of three offspring from normal parentage.

REFERENCES

1. Smith, D. W., Theiler, K., and Schachenmann, G.: Rib-gap defect with micrognathia, malformed tracheal cartilages, and redundant skin: A new pattern of defective development. J. Pediatr., *69*:799, 1966.
2. Doyle, J. F.: The skeletal defects of the cerebro-costo-mandibular syndrome. Ir. J. Med. Sci., Ser. 7, *2*:595, 1969.
3. McNicholl, B., Egan-Mitchell, B., Murray, J. P., Doyle, J. F., Kennedy, J. D., and Crome, L.: Cerebro-costo-mandibular syndrome. A new familial developmental disorder. Arch. Dis. Child., *45*:421, 1970.







Left, Newborn showing severe micrognathia and incompletely ossified aberrant ribs. (From Smith, D. W., et al.: J. Pediatr., *69*:799, 1966.) *Right,* Four year old. (From McNicholl, B., et al.: Arch. Dis. Child., *45*:421, 1970.)

LEPRECHAUNISM SYNDROME
(Donohue Syndrome)

Prenatal Adipose Deficiency, Full Lips, Enlarged Phallus

This somewhat puzzling disorder was initially described as dysendocrinism by Donohue[1] in 1948. Later Donohue and Uchida[2] reported two siblings under the term leprechaunism and since then more than 14 cases have been recorded.

ABNORMALITIES

Growth. Prenatal growth deficiency with retarded osseous maturation and marked lack of adipose tissue; mean birth weight, about 2.6 kg.

Facies. Small with prominent eyes, wide nostrils, thick lips, large ears.

Endocrine. Large phallus, breast hyperplasia in female, Leydig cell hyperplasia (male), follicular development with cystic ovary, increased pituitary gonadotropes, hyperplasia of islets of Langerhans.

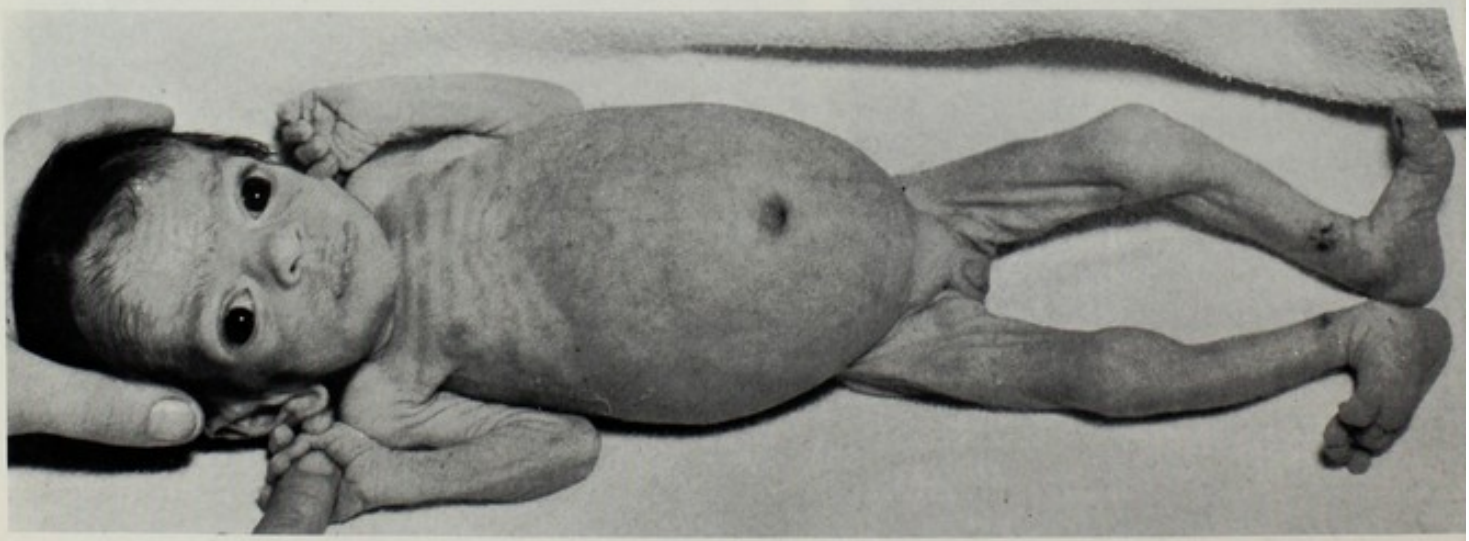
Other. Body and facial hirsutism. Apparent motor and mental retardation. Iron deposition in liver.

NATURAL HISTORY. Usually severe failure to thrive and frequent infections with death in early infancy. One patient survived to two and one fourth years of age. Hypoglycemia occurs following prolonged fast. The basic defect in metabolism is undetermined.

ETIOLOGY. Autosomal recessive inheritance is implied by consanguinity and sibship occurrence.

REFERENCES

1. Donohue, W. L.: Dysendocrinism. J. Pediatr., *32*:739, 1948.
2. Donohue, W. L., and Uchida, I.: Leprechaunism. A euphuism for a rare familial disorder. J. Pediatr., *45*:505, 1954.
3. Salmon, M. A., and Webb, J. N.: Dystrophic changes associated with leprechaunism in a male infant. Arch. Dis. Child. *38*:530, 1963.
4. Rogers, D. R.: Leprechaunism (Donohue's syndrome). A possible case, with emphasis on changes in the adenohypophysis. Am. J. Clin. Path., *45*:614, 1966.



Six week old; birth weight, 3 pounds, 14 ounces. (From Donohue, W. L., and Uchida, I.: J. Pediat., *45*:505, 1954.)

BERARDINELLI LIPODYSTROPHY SYNDROME
(Generalized Lipodystrophy)

Lipoatrophy, Phallic Hypertrophy, Hepatomegaly and Hyperlipemia

Berardinelli[1] reported this unusual lipodystrophic syndrome in 1954. Although more than 25 cases have subsequently been recorded, the metabolic defect responsible for this inborn error of metabolism has not been determined.

ABNORMALITIES

Performance. Mental deficiency as a variable feature.

Growth. Accelerated growth and maturation, enlargement of hands and feet, phallic enlargement, hypertrophy of muscle with excess glycogen, lack of adipose from early life.

Skin. Coarse with hyperpigmentation, especially in axillae. Variable acanthosis nigricans.

Hair. Hirsutism with curly scalp hair.

Vessels. Large superficial veins.

Liver. Hepatomegaly with excess neutral fat, glycogen, and eventual cirrhosis.

Plasma. Hyperlipidemia (neutral fats). Hyperinsulinism. Insulin-resistant nonketotic hyperglycemia may develop.

OCCASIONAL ABNORMALITIES. Cardiomegaly, corneal opacities, hyperproteinemia, hyperinsulinemia.

NATURAL HISTORY. The accelerated growth and hyperlipidemia are most prominent in early childhood and hyperglycemia may develop in later childhood. The oldest reported patient, 16 years of age, was diabetic. Cirrhosis of the liver with esophageal varices may become a fatal complication.

COMMENT. Although the accelerated growth and maturation plus the muscle hypertrophy and enlargement of the phallus are suggestive of androgen effect, neither androgens nor gonadotropins are elevated and the hirsutism does not include pubic and axillary hair. Mabry, et al.[4] found that pituitary and target endocrine gland studies were near-normal. They found higher levels for several hypothalamic-releasing factors (corticotropin releasing factor, follicle-stimulating hormone releasing factor, and melanocyte stimulating hormone releasing factor) than found in controls; the explanation for this intriguing observation remains to be determined.

ETIOLOGY. Autosomal recessive as indicated by sibship occurrence and parental consanguinity.

REFERENCES

1. Berardinelli, W.: An undiagnosed endocrinometabolic syndrome: report of two cases. J. Clin. Endocrinol. Metab., *14*:193, 1954.
2. Seip, M., and Trygstad, O.: Generalized lipodystrophy. Arch. Dis. Child., *38*:447, 1963.
3. Senior, B., and Gellis, S. S.: The syndromes of total lipodystrophy and of partial lipodystrophy. Pediatrics, *33*:593, 1964.
4. Mabry, C. C., Hollingsworth, D. R., Upton, G. V., and Corbin, A.: Pituitary-hypothalamic dysfunction in generalized lipodystrophy. J. Pediatr., *82*:625, 1973.



Preadolescent age boy showing hypertrophied muscle and relative lack of subcutaneous fat. (Courtesy of Central Wisconsin Colony and Training School.)

CUTIS LAXA-GROWTH DEFICIENCY SYNDROME

Cutis Laxa, Lax Joints, Growth Deficiency

Six cases of this disorder have been reported[1-3] and recently summarized by Reisner, et al.[3]

ABNORMALITIES

Growth. Prenatal growth deficiency with full-term birth weights of 1.75 to 2.5 kg and lengths from 43 to 46 cm.

Skin. Cutis laxa with diminished elastic fibers on biopsy.

Joints. Lax joints, congenital dislocation of hip.

Other Features of Uncertain Frequency: Large fontanels, low-set ears, coloboma of macula, slow developmental progress.

NATURAL HISTORY. Remains to be determined.

ETIOLOGY. Presumed autosomal recessive because of sibship occurrence, and consanguinity in one case.

REFERENCES

1. Fittke, H.: Über eine ungewöhnliche Form "Multipler Erbabartung" (Chalodermie und Dysostose). Z. Kinderheilkd., *63*:510, 1943.
2. Bittel-Dobrzynska, N., and Siniecki, B.: Cutis laxa (Ehlers-Danlos syndrome) with congenital dislocation of the hips. Endokrynol. Pol., *15*:469, 1964.
3. Reisner, S. H., Seelenfreund, M., and Ben-Bassat, M.: Cutis laxa associated with severe intrauterine growth retardation and congenital dislocation of the hip. Acta Paediatr. Scand., *60*:357, 1971.



Infant with cutis laxa, prenatal onset growth deficiency, and dislocation of the hip. (From Reisner, S. H., et al.: Acta Paediatr. Scand., *60*:357, 1971.)

DISTICHIASIS-LYMPHEDEMA SYNDROME

Double Row of Eyelashes, Lymphedema

ABNORMALITIES[1-3]

Eye. Extra row of eyelashes, replacing meibomian glands.

Limb. Lymphedema, predominantly from knee downward.

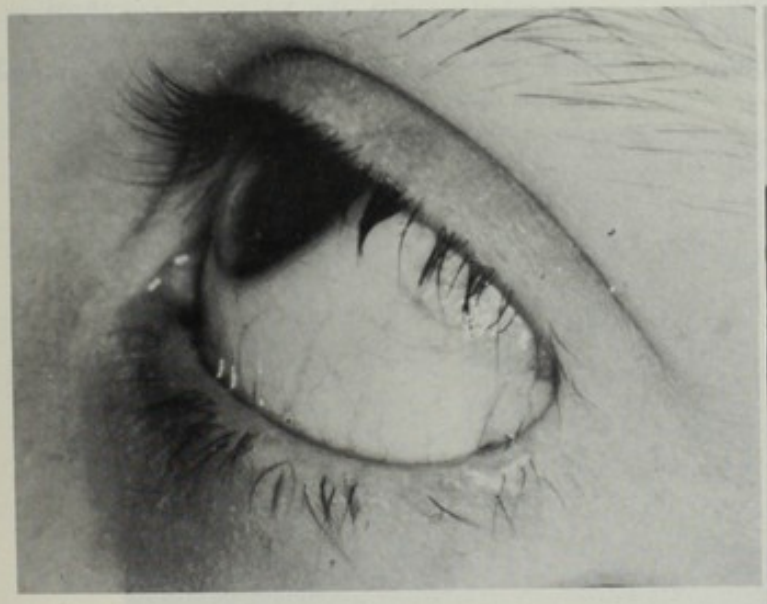
OCCASIONAL OR UNCERTAIN FREQUENCY. Epidural spinal cysts +/− secondary vertebral anomalies. Partial ectropion of lower lid, epicanthal folds, pterygium colli.

NATURAL HISTORY. The extra eyelashes may cause irritative ocular problems. The lymphedema usually becomes evident between five and 20 years, especially at the time of adolescence. Epidural cysts with secondary neurologic or other complications must always be considered in this disorder. Eyelash removal or surgery for the lymphedema are difficult to accomplish with good results and hence treatment is generally held back unless grossly indicated.

ETIOLOGY. Autosomal dominant inheritance.

REFERENCES

1. Falls, H. F. and Dertesz, E. D.: A new syndrome combining pterygium colli with developmental anomalies of the eyelids and lymphatics of the lower extremities. Trans. Am. Ophthalmol. Soc., *62*: 248, 1964.
2. Robinow, M., Johnson, G. F., and Verhagen, A. D.: Distichiasis-lymphedema. A hereditary syndrome of multiple congenital defects. Am. J. Dis. Child., *119*:343, 1970.
3. Hoover, R. E., and Kelley, J. S.: Distichiasis and lymphedema: A hereditary syndrome with possible multiple defects—A report of a family. Trans. Ophthalmol. Soc., *69*:293, 1971.





Distichiasis in the eye of this teen-age girl and lymphedema in her leg *(on right)* and more severely so in that of her affected mother *(on left)*.

FABRY SYNDROME

(Anderson-Fabry Disease, Angiokeratoma Corporis Diffusum)

Dark Nodular Angiectases, Attacks of Burning Pain, Renal Insufficiency

This disease was originally described by Fabry.[1] Its basis has recently been recognized as the cellular accumulation of ceramidetrihexoside as a consequence of the deficiency of ceramidetrihexosidase, the enzyme that normally degrades this neutral glycolipid.[2]

ABNORMALITIES IN AFFECTED MALES[3]

General. Attacks of burning pain in hands and feet.

Cutaneous. Minute dark nodular angiectases in clusters around umbilicus, on genitalia, knees, hips, mucous membranes, etc.

Eye. Superficial corneal opacities.

Renal. Proteinuria; variable red cells, white cells, and casts in urine; progressive renal insufficiency.

Central Nervous System. May have seizures, headache, dizziness, hemiplegia, other presumed reactions to cerebrovascular disease.

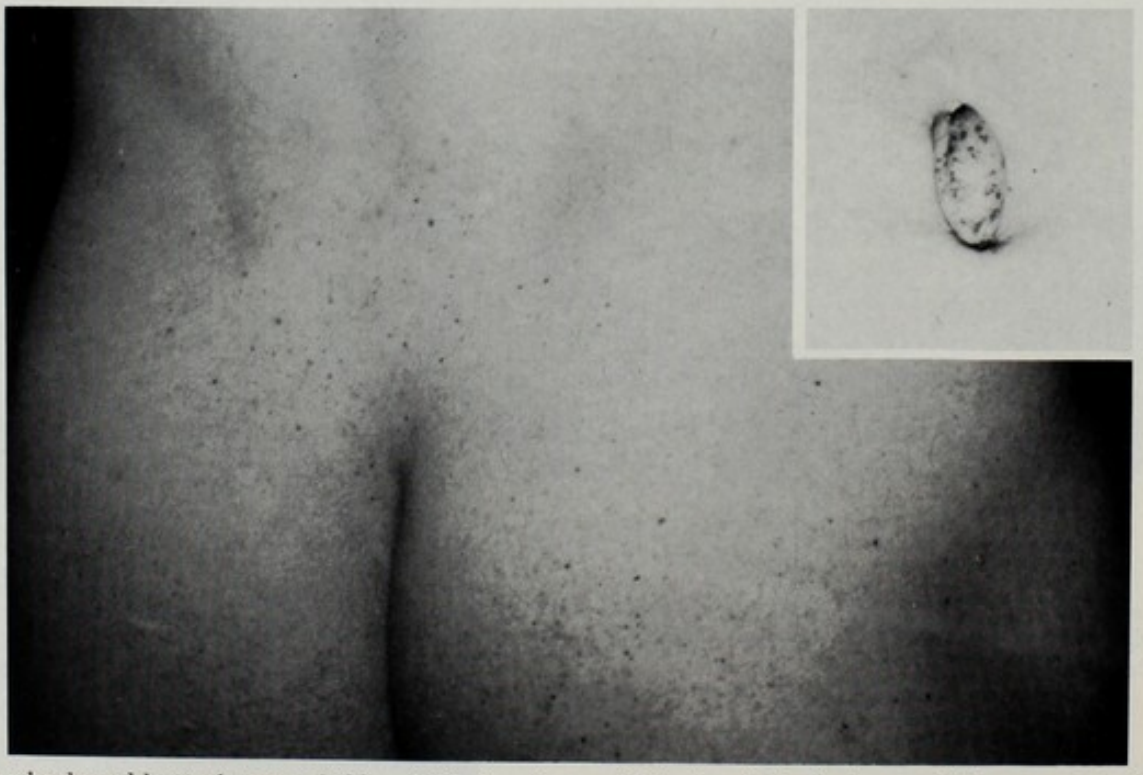
OCCASIONAL ABNORMALITIES. Diarrhea, epistaxes, hemoptysis, anemia secondary to blood loss, saccular retinal vessels, coronary disease, varicosities, edema of ankles, hands, and face, hypohidrosis. Central nervous system problems may include mental deficiency, optic atrophy, myoclonus, spastic paraplegia, and/or dementia. Thick lips, coarse facies.

NATURAL HISTORY. The skin angiectases, though often present in earlier childhood, are usually not noted until after ten years of age. The burning pain, sometimes associated with fever, may start in childhood; it occurs in attacks precipitated by heat, cold, exercise, or fever. Renal insufficiency progresses to a fixed specific gravity of the urine, and the mean age of survival is 42 years.

ETIOLOGY. X-linked with full penetrance in the hemizygous male and variable mild expressivity in the heterozygous female who may show mild corneal opacities and has a value of ceramidetrihexosidase which is intermediary between that of the affected male and the normal.

REFERENCES

1. Fabry, J.: Ein Beitrag zur Purpura haemorrhagica nodularis. Arch. Derm. Syph., *43*:187, 1898.
2. Brady, R. O., Gal, A. E., Bradley, R. M., Martensson, E., Warshaw, A. L., and Laster, L.: Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N. Engl. J. Med., *276*:1163, 1967.
3. Optiz, J. M., et al.: The genetics of angiokeratoma corporis diffusum (Fabry's disease) and its linkage relations with the Xg locus. Am. J. Hum. Genet., *17*:325, 1965.
4. Wallace, H. G.: Anderson-Fabry disease. Br. J. Dermatol., *88*:1, 1973.



Lower back and buttock area of older child showing small dark nodular lesions, which are especially prominent in the umbilicus (inset). (From R. Summitt, University of Tennessee Medical School.)

RILEY-DAY SYNDROME
(Familial Dysautonomia)

Dysautonomia, Poor Coordination, Lack of Tearing

Multiple indications of autonomic dysfunction were first noted in this condition by Riley, Day and others.[1] Brunt and McKusick[2] have reported the findings in 172 families.

ABNORMALITIES

Evidences of Dysautonomia. Swallowing difficulty in infancy, aspiration, cyclic vomiting, diarrhea.
Emotional lability, breath holding.
Skin blotching, hyperhidrosis.
Insensitivity to pain; may develop Charcot neuropathic knee joint.
Lack of tearing; may develop corneal ulcer.
Taste deficiency, decreased fungiform and circumvallate papillae.
Unstable temperature, unexplained bouts of fever.
Labile blood pressure.
Urinary frequency.
Absent deep tendon reflexes.
Poor coordination; scoliosis often develops at eight to ten years.
Absence of flare response to cutaneous histamine.
Exaggerated response to norepinephrine.

Other. Small stature is a variable feature, often of prenatal onset. Mental deficiency occurs in 55 per cent and seizures in 50 per cent.

OCCASIONAL ABNORMALITIES. Microcephaly, hydrocephalus, craniofacial disproportion (small face), congenital heart defect, dislocation of hip, pes cavus, megacolon, megaesophagus.

NATURAL HISTORY. Failure to thrive is the rule in infancy, with aspiration and pneumonia being the chief causes of death. These are often related to swallowing difficulty, which appears to be secondary to involvement of the nucleus ambiguus. Hypotension and/or cardiac arrest are hazards with general anesthesia in these patients. One fourth die before ten years of age and one half before 22 years.

ETIOLOGY. Autosomal recessive, especially in Ashkenazic Jews. Hypoplasia of autonomic ganglia with cytologic changes in hypothalamus, brain stem, and autonomic ganglia.

REFERENCES

1. Riley, C. M., Day, R. L., Greeley, D. McL., and Langford, W. S.: Central autonomic dysfunction with defective lacrimation. I. Report of five cases. Pediatrics, *3*:468, 1949.
2. Brunt, P. W., and McKusick, V. A.: Familial dysautonomia. Medicine, *49*:343, 1970.

SCHWACHMAN SYNDROME

Lack of Exocrine Pancreas, Leukopenia

In 1963 Schwachman, et al.[1] described five children with evidence of pancreatic insufficiency and leukopenia, none of whom had cystic fibrosis of the pancreas. A total of at least 39 cases have been documented.

ABNORMALITIES. Lack of exocrine pancreas, which is replaced by adipose tissue. Pancreatic trypsin, lipase, and amylase are absent.

Leukopenia, variable in degree.

Mild skeletal changes, such as: metaphyseal chondrodysplasia, focal lack of mineralization in epiphyses, and narrow sacroiliac notch.

OCCASIONAL ABNORMALITIES. Anemia, thrombocytopenia, eczema, immunoglobulin deficiency; one patient developed leukemia.

NATURAL HISTORY. Failure to thrive with diarrhea is the most common presenting situation at two to ten months of age. Of interest is the observation that there is no steatorrhea; presumably the intestinal lipases are adequate in the absence of pancreatic lipase. Viscosity of duodenal secretions is also normal in contrast to cystic fibrosis of the pancreas which can be readily excluded by sweat electrolyte studies. The diarrhea tends to improve with age even without pancreatic replacement therapy. The latter therapy is followed by dramatic response in some patients but not in others. The leukopenia is variable from time to time and may be accompanied by a high frequency of bacterial infections.

ETIOLOGY. Presumed autosomal recessive.

COMMENT. The exocrine pancreas is replaced by adipose tissue, whereas the islet cells of Langerhans are intact. Both are derived from a common endodermal outpouching from the foregut, and therefore it is assumed that the exocrine pancreatic cells are lost early in life and replaced by fat. One possibility is a defect in the integrity of the lysozymes in these cells, allowing the cells to be destroyed by the very enzymes they produce.

REFERENCES

1. Schwachman, H., Diamond, L. K., Oski, F. A., and Khaw, K.-T.: Pancreatic insufficiency and bone marrow dysfunction. A new clinical entity. J. Pediatr., *63*:835, 1963.
2. Burke, V., Colebatch, J. H., Anderson, C. M., and Simons, M. J.: Association of pancreatic insufficiency and chronic neutropenia in childhood. Arch. Dis. Child., *42*:147, 1967.
3. McLennan, T. W., and Steinbach, H. L.: Schwachman's syndrome: The broad spectrum of bony abnormalities. Radiology, *112*:167, 1974.

WISKOTT-ALDRICH SYNDROME

Thrombocytopenia, Eczema, Immunological Deficiency

Wiskott[1] described three brothers in 1937 with eczema, thrombocytopenia, and frequent infections, a similar pattern to that noted 17 years later by Aldrich, et al.[2] who recognized the X-linked mode of inheritance of this condition. It has been reported in at least 57 boys.[3]

ABNORMALITIES. Thrombocytopenia from early infancy causing melena and purpura. Megalokaryocytes usually diminished.

Immunological deficiency with frequent infections, especially of skin, middle ear, sinuses, and lung. Impaired delayed hypersensitivity.

Often hypoplastic thymus, diminished lymphocytes, low gamma M with elevated gamma A, elevated gamma E, and low isoagglutinins.

Eczema, especially in infancy.

OCCASIONAL ABNORMALITIES. Eosinophilia, leukocytosis with myeloid hyperplasia, anemia, hypoaminoaciduria, joint effusions, and development of malignancy such as reticuloendotheliosis, reticulum cell sarcoma, astrocytoma, malignant lymphoma, or myelogenous leukemia. Cortical hyperostosis (mandible, clavicle).

NATURAL HISTORY. Most patients die in infancy or childhood from the consequences of bleeding, infection, or malignant neoplasia. Therapeutic endeavors with splenectomy, hydrocortisone analogue, or gamma globulin have been met with no appreciable improvement. The oldest survivor is 15 years.[3]

ETIOLOGY. X-linked recessive.

REFERENCES

1. Wiskott, A.: Familiärer angeborener Morbus Werlhofii? Monatsschr. Kinderheilkd., *68*:212, 1937.
2. Aldrich, R. A., Steinberg, A. G., and Campbell, D. C.: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics, *13*:133, 1954.
3. Wolff, J. A.: Wiskott-Aldrich syndrome: clinical, immunologic, and pathologic observations. J. Pediatr., *70*:221, 1967.

S. Miscellaneous Syndromes

CHEDIAK-HIGASHI SYNDROME

Partial Albinism, Large Granules in Leukocytes

César[1] originally described this disorder in 1943, and later Chediak[2] and Higashi each independently recognized the disease. More than 40 cases have been reported.

ABNORMALITIES

Partial Albinism. Gray sheen to light-colored hair, diminished uveal and retinal pigmentation with photophobia and nystagmus.

Hematologic and Reticuloendothelial. Neutropenia with tendency toward lymphocytosis, anemia, and thrombocytopenia. Large cytoplasmic inclusions in leukocytes, promyeloblasts, myeloblasts, and other granule-containing cells. Lymphoid-histiocytic cell infiltration with variable hepatosplenomegaly and lymphadenopathy.

OCCASIONAL ABNORMALITIES. Mental deficiency, seizures, peripheral neuropathy; corneal opacity; hyperhidrosis; buccal ulcerations; neonatal icterus; hyperlipemia.

NATURAL HISTORY. The majority of affected individuals die in early childhood as the result of recurring infection or a peculiar malignant lymphoma. Survival to adulthood can occur, but is unusual.

ETIOLOGY. Autosomal recessive with high frequency of consanguinity. The heterozygote may show enlarged cytoplasmic inclusions in leukocytes.

COMMENT. Electron microscopy has provided evidence for the leukocyte cytoplasmic granules being swollen lysosomes; the melanocytes contain giant melanosomes, which may explain the partial albinism. Windhorst, et al.[3] have interpreted this evidence as being indicative of a disease of limiting membranes.

REFERENCES

1. César, A. B.: Neutropenia crónica maligna familiar con granulaciones atípicas de los leucocitos. Bol. Soc. Cub. Ped., *15*:900, 1953.
2. Chediak, M.: Nouvelle anomalie leucocytaire de caractère constitutionnel et familial. Rev. Hematol., *7*:362, 1952.
3. Windhorst, D. B., Zelickson, A. S., and Good, R. A.: Chediak-Higashi syndrome: hereditary gigantism of cytoplasmic organelles. Science, *151*:81, 1966.
4. Blume, R. S., and Wolff, S. M.: The Chediak-Higashi syndrome; Studies in four patients and review of the literature. Medicine, *51*:247, 1972.

LATERALITY ANOMALADS

In addition to reversal of the sides, with partial to complete situs inversus, there can be bilateral left- or right-sidedness.

The primary defect in the following disorders is a failure of normal asymmetry in morphogenesis. The basic problem would presumably be present prior to 30 days of development. The accompanying chart sets forth the differences as well as the similarities between the patterns due to predominantly left-sided bilaterality and due to right-sided bilaterality. Among other differences, the spleen dramatically reflects the variant laterality in the two disorders. With left-sided bilaterality there is polysplenia (usually bilateral spleens plus rudimentary extra splenic tissue) and with right-sided bilaterality there is asplenia or a hypoplastic spleen. As might be anticipated for single primary defects, there is considerable variability between cases in terms of severity. Both tend to be sporadic occurrences, with rare exception. They may occur as one aspect of the Kartagener syndrome (situs inversus, sinusitis, and bronchiectasis).

A. BILATERAL LEFT-SIDEDNESS ANOMALAD (Polysplenia syndrome). The sex incidence is about equal. The cardiac anomalies are usually not as severe as with bilateral right-sidedness.

B. BILATERAL RIGHT-SIDEDNESS ANOMALAD (Asplenia syndrome, Ivemark syndrome, triad of spleen agenesis, defects of heart and vessels and situs inversus). This is two to three times more common in males than females. The complex cardiac anomalies, usually giving rise to cyanosis and early cardiac failure, are the major cause of early death. The possibility of gastrointestinal problems must also be considered, especially related to the aberrant mesenteric attachments. Renal anomalies are also more frequent (25 per cent). Survivors have had an increased frequency of cutaneous, respiratory, and other infections, possibly related to the asplenia. Tests to suggest asplenia include evaluation of red blood cells for Howell-Jolly bodies and Heinz bodies.

REFERENCES

1. Van Mierop, L. H. S., Gessner, I. H., and Schiebler, G. L.: Asplenia and polysplenia syndromes. Birth Defects, *8*:74, 1972.
2. Freedom, R. M.: The asplenia syndrome. J. Pediatr., *81*:1130, 1972.
3. Rogers, J.: Personal communication.

T. Miscellaneous Anomalads

KARTAGENER SYNDROME

Situs Inversus, Sinusitis, Bronchiectasis

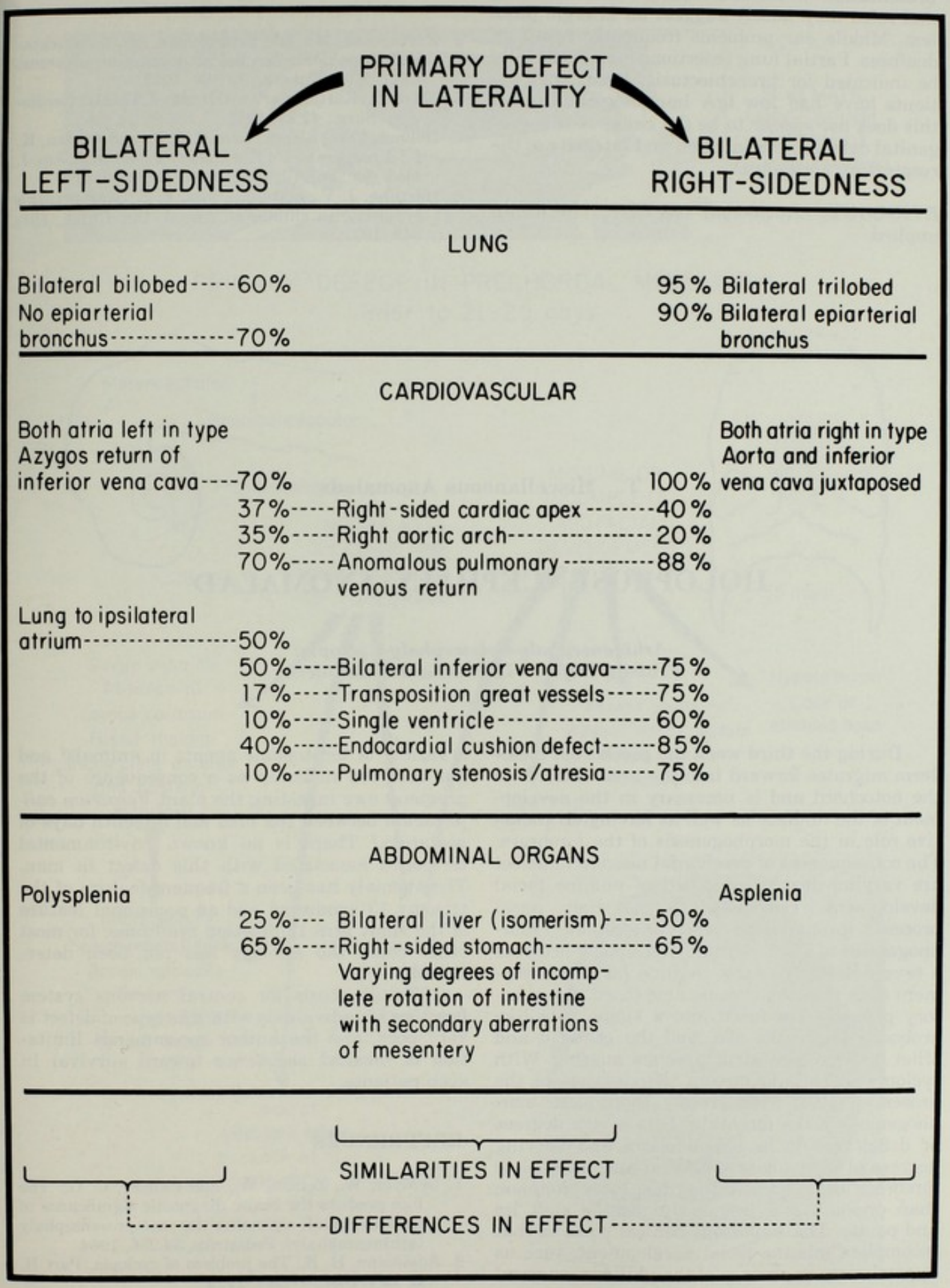
Described by Kartagener[1] in 1933, this syndrome accounts for about one tenth of the cases of bronchiectasis and about one sixth of the cases of situs inversus.

ABNORMALITIES[1-4]

Organ Orientation. Situs inversus, partial to complete, with gross defects in cardiac septation in some patients and occasional asplenia. (See Laterality Anomalads, above.)

Respiratory Tract. Absence of frontal sinus development. Thick tenacious mucus with problems of infection and stasis.

NATURAL HISTORY. Providing the patient does not have a lethal cardiac anomaly, there is variable age of onset and severity of chronic middle ear infection, rhinitis (sometimes with nasal polyps), sinusitis, pneumonia, chronic cough, and follicular bronchiectasis. *H. influenzae* and *D. pneumoniae* are the more common bacterial pathogens. Over 90 per cent of patients


PRIMARY DEFECT IN LATERALITY
BILATERAL LEFT-SIDEDNESS
BILATERAL RIGHT-SIDEDNESS
LUNG
Bilateral bilobed 60%
No epiarterial bronchus 70%
95% Bilateral trilobed
90% Bilateral epiarterial bronchus
CARDIOVASCULAR
Both atria left in type
Azygos return of inferior vena cava 70%
100%
Both atria right in type
Aorta and inferior vena cava juxtaposed
37% Right-sided cardiac apex 40%
35% Right aortic arch 20%
70% Anomalous pulmonary venous return 88%
Lung to ipsilateral atrium 50%
50% Bilateral inferior vena cava 75%
17% Transposition great vessels 75%
10% Single ventricle 60%
40% Endocardial cushion defect 85%
10% Pulmonary stenosis/atresia 75%
ABDOMINAL ORGANS
Polysplenia
Asplenia
25% Bilateral liver (isomerism) 50%
65% Right-sided stomach 65%
Varying degrees of incomplete rotation of intestine with secondary aberrations of mesentery
SIMILARITIES IN EFFECT
DIFFERENCES IN EFFECT

are symptomatic during childhood. The initial presentation of chronic rhinitis with wheezing and rales may falsely suggest an allergic problem. Middle ear problems frequently result in deafness. Partial lung resections may eventually be indicated for bronchiectasis. Occasional patients have had low IgA immunoglobulin, but this does *not* appear to be the cause of this congenital defect in the function and integrity of the respiratory epithelium.

ETIOLOGY. Autosomal recessive inheritance implied.

REFERENCES

1. Kartagener, M.: Zur pathogenese der bronkiektasien. Bronkiektasien bei situs viscerum inversus. Beitr. Klin. Tuberk., *83*:489, 1933.
2. Mayo, P.: Kartagener's syndrome. J. Thorac. Cardiovasc. Surg., *42*:39, 1961.
3. Holmes, L. B., Blennerhassett, J. B., and Austen, K. F.: A reappraisal of Kartagener's syndrome. Am. J. Med. Sci., *255*:13, 1968.
4. Hartline, J. V., and Zelkowitz, P. S.: Kartagener's syndrome in childhood. Am. J. Dis. Child., *121*: 349, 1971.

T. Miscellaneous Anomalads

HOLOPROSENCEPHALY ANOMALAD

Arhinencephaly-Cebocephaly-Cyclopia:
Primary Defect—In Prechordal Mesoderm

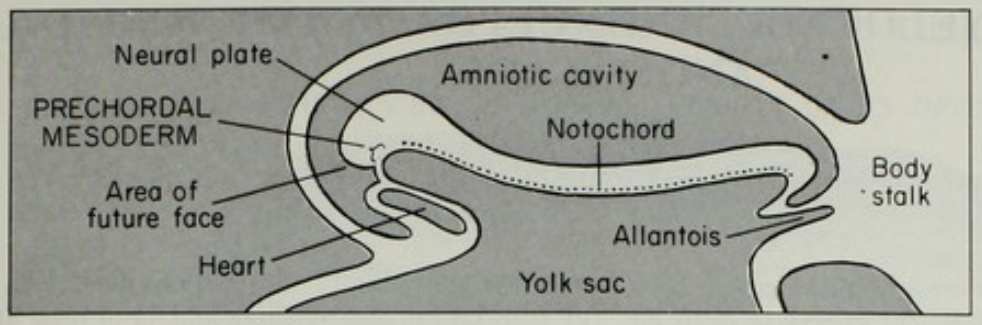
During the third week the prechordal mesoderm migrates forward into the area anterior to the notochord and is necessary in the development of the midface as well as having an inductive role in the morphogenesis of the forebrain. The consequences of prechordal mesoderm defect are varying degrees of deficit of midline facial development, especially the median nasal process (premaxilla), and incomplete morphogenesis of the forebrain. Cyclopia represents a severe deficit in early midline facial development such that the eyes become fused, the olfactory placodes are fused into a single tube-like proboscis above the eye, and the ethmoid and other midline bony structures are missing. With cyclopia there is failure in the cleavage of the prosencephalon, with grossly incomplete morphogenesis of the forebrain. Less severe degrees of deficit result in hypotelorism and varying degrees of inadequate midfacial and incomplete forebrain development that are more common than cyclopia and frequently include cleft lip and palate. The important clinical point is that incomplete midline facial development, such as hypotelorism or absence of the philtrum or nasal septum, suggests the possibility of a serious anomaly in brain development and function.

This type of anomalad has been produced by a variety of teratogenic agents in animals[2] and has occurred in sheep as a consequence of the pregnant ewe ingesting the plant *Veratrum californicum* between the fifth and fifteenth days of gestation.[3] There is no known environmental teratogen associated with this defect in man. The anomaly has been a frequent feature of the trisomy 13 syndrome and an occasional feature of the short arm 18 deletion syndrome; for most other cases the etiology has not been determined.

The prognosis for central nervous system function in individuals with this type of defect is very poor, and the author recommends limitation of medical assistance toward survival in such patients.

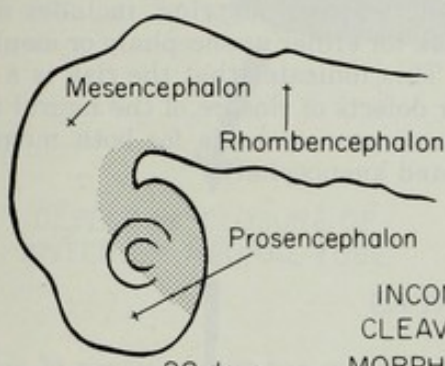
REFERENCES

1. DeMyer, W., Zeman, W., and Palmer, C. G.: The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics, *34*:256, 1964.
2. Adelmann, H. B.: The problem of cyclopia. Part II. Q. Rev. Biol., *11*:284, 1936.
3. Babbott, F. L., Binns, W., and Ingalls, T. H.: Field studies of cyclopian malformations in sheep. Arch. Environ. Health, *5*:109, 1962.



SCHEMATIC LONGITUDINAL SECTION OF 21=DAY EMBRYO

PRIMARY DEFECT IN PRECHORDAL MESODERM
Prior to 21-25 days



28 days



35 days

INCOMPLETE CLEAVAGE AND MORPHOGENESIS OF FOREBRAIN

MISSING OR INCOMPLETE MIDFACIAL DEVELOPMENT

Single ventricle
Absence of corpus callosum
Fused thalami
Incomplete anterior and posterior pituitary

Microcephaly
Severe mental defect
Apneic episodes
Seizures
Abnormal EEG
Infant death

Lack of olfactory lobes
Lack of optic nerve

Cyclopia
Anophthalmia
Microphthalmia
Coloboma, iris
Retinal defect

Cleft lip
Cleft palate

Absent philtrum
Absent nasal septum
Single naris
Proboscis

Hypotelorism
Lack of ethmoid bone



MENINGOMYELOCELE, ANENCEPHALY, INIENCEPHALY ANOMALADS

Primary Defect—In Neural Tube Closure

The initiating malformation appears to be a defect in closure of the neural groove to form an intact neural tube, which is normally completely fused by 28 days. Anencephaly represents a defect in closure at the anterior portion of the neural groove. The secondary consequences are as follows: (1) the unfused forebrain develops partially and then tends to degenerate; (2) the calvarium is incompletely developed; and (3) the facial features and auricular development are secondarily altered to a variable degree, including cleft in the palate, frequent abnormality of the cervical vertebrae, and occasional incomplete development of the anterior pituitary.

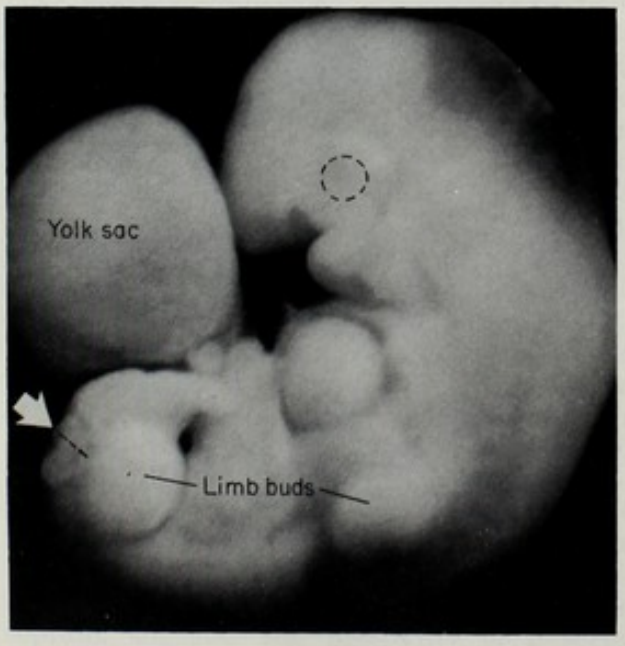
Defects of closure at the mid- or caudal neural groove can give rise to meningomyelocele and other secondary defects, as depicted. The early form of one such lesion is illustrated below.

Defects of closure in the cervical and upper thoracic region can culminate in the iniencephaly anomalad in which secondary features may include retroflexion of the upper spine with short neck and trunk, cervical and upper thoracic vertebral anomalies, defects of thoracic cage, anterior spina bifida, diaphragmatic defects with or without hernia, and hypoplasia of lung and/or heart.

The recurrence risk for defects of neural tube closure, about 5 per cent for parents who have had one affected offspring, includes about an equal risk for either anencephaly or meningomyelocele. This indicates that the risk is a general one for defects of closure of the neural tube, the presumed common basis for both meningomyelocele and anencephaly.

REFERENCES

1. Giroud, A.: Causes and morphogenesis of anencephaly. Ciba Foundation Symposium on Congenital Malformations, 1960, pp. 199–218.
2. Lemire, R. J., Shepard, T. H., and Alvord, E. C., Jr.: Caudal myeloschisis (lumbo-sacral spina bifida cystica) in a five millimeter (horizon XIV) human embryo. Anat. Rec., *152*:9, 1965.
3. Lemire, R. J., Beckwith, J. B., and Shepard, T. H.: Iniencephaly and anencephaly with spinal retroflexion. Teratology, *6*:27, 1972.

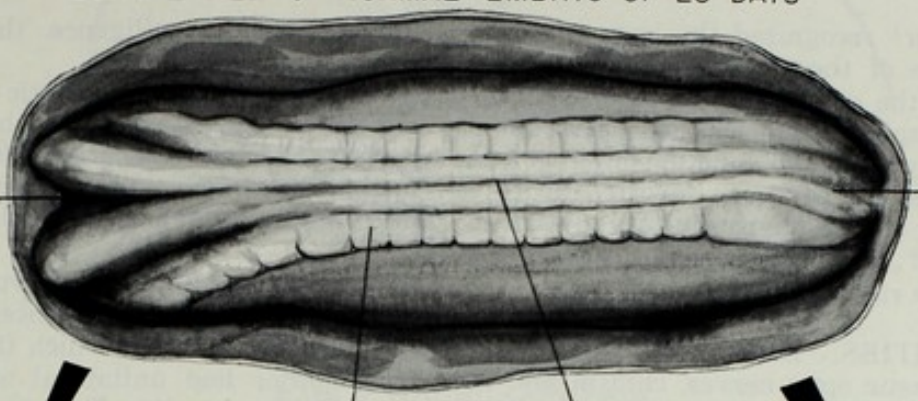




Otherwise normal 28-day embryo with incomplete closure of the posterior neural groove (arrow), which shows aberrant growth of cells to the side in a transverse section (lower). Had this embryo survived, it would presumably have developed a meningomyelocele. (From Lemire, R.: Anat. Rec., *152*:9, 1965.)

DEFECTS IN CLOSURE OF NEURAL TUBE

DORSAL VIEW OF NORMAL EMBRYO OF 23 DAYS



DEFECT IN CLOSURE OF ANTERIOR NEURAL TUBE

1. Incomplete development of brain with degeneration
2. Incomplete development of calvaria
3. Alteration in facies +/− auricle



Anencephaly

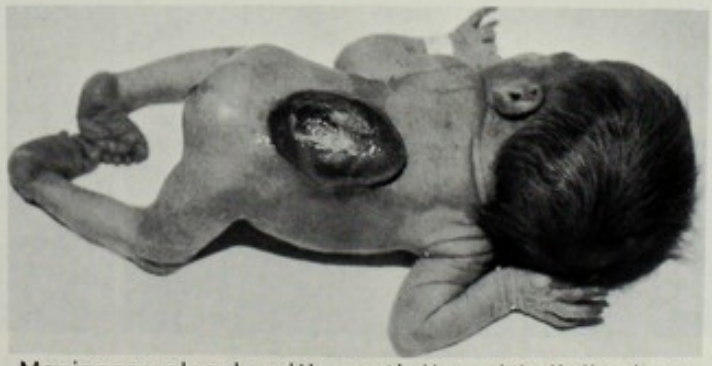
DEFECT IN CLOSURE



Neural deficit caudal to lesion → +/− Club foot

Meningomyelocele → +/− Hydrocephalus

Defect in spinous process → Spina bifida



Meningomyelocele with partially epithelialized sac

SEPTO-OPTIC DYSPLASIA ANOMALAD

de Morsier[1] recognized the association between absence of the septum pellucidum and hypoplasia of the optic nerves and termed this septo-optic dysplasia. The clinical spectrum of altered development and function arising from this defect has recently been reported by Hoyt and others to include hypopituitary dwarfism. The presumed developmental pathogenesis is depicted to the right.

ABNORMALITIES. Based on 17 cases.[2-4]

Eye. Hypoplastic optic nerves, chiasm and infundibulum with pendular nystagmus and visual impairment, occasionally including field defects.

Hypothalamic. Secondary hypopituitarism, varying from isolated growth hormone deficiency to panhypopituitarism.

Other. Agenesis of septum pellucidum in about half of cases.

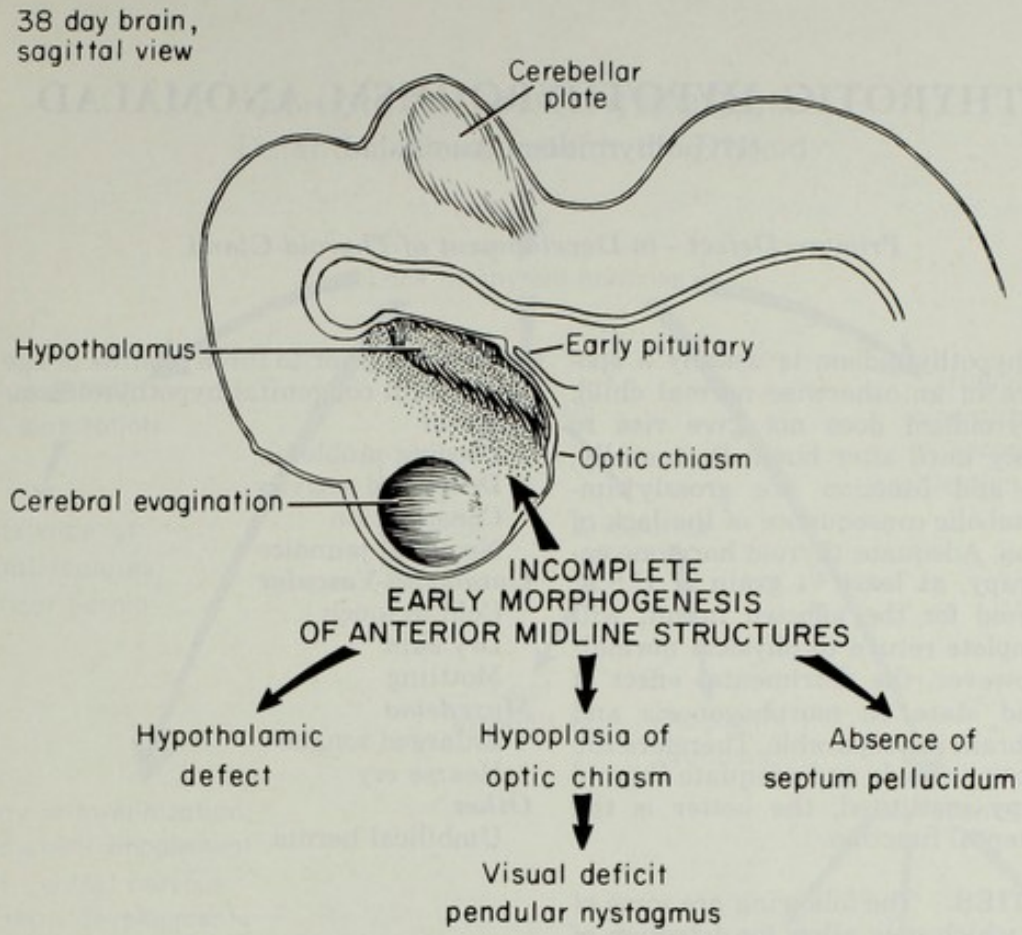
NATURAL HISTORY. Visual impairment, including partial to complete amblyopia, is frequent, and funduscopic evaluation discloses hypoplastic optic discs. Hypopituitarism of hypothalamic origin is a frequent feature and merits replacement therapy. Kaplan found this anomalad to be the most frequent recognized single defect in children with pituitary growth hormone deficiency. Most affected individuals are of normal intelligence, though some have mild mental deficiency.

Features of the septo-optic dysplasia anomalad may occur as a part of a broader pattern of early brain defect such as in the holoprosencephaly type of defect, in which case the prognosis for brain function and survival is poor.

ETIOLOGY. Unknown. Though this defect is usually a sporadic occurrence, the author has evaluated one case in which the otherwise normal mother had unilateral amblyopia with a hypoplastic optic disc. Therefore first degree relatives should be evaluated, especially in terms of funduscopic examination.

REFERENCES

1. de Morsier, G.: Études sur les dysraphies crânio-encéphaliques. III. Agénésie du septum lucidum avec malformation du tractus optique. La dysplasie septo-optique. Schweiz. Arch. Neurol. Neurochir. Psychiatr., *77*:267, 1956.
2. Hoyt, W. F., Kaplan, S. L., Grumbach, M. M., and Glaser, J. S.: Septo-optic dysplasia and pituitary dwarfism. Lancet, *1*:893, 1970.
3. Kaplan, Selma, University of California School of Medicine, San Francisco, personal communication.
4. Brook, C. G. D., Sanders, M. D., and Hoare, R. D.: Septo-optic dysplasia. Br. Med. J., *3*:811, 1972.





Above, Presumed localization of early single defect (stippled area) as shown in sagittal view of 38-day brain.
Below, Photos of retinae of four year old patient with the septo-optic dysplasia anomalad who had reduced vision, pendular nystagmus, and growth deficiency secondary to pituitary growth hormone deficiency. Note the hypoplastic optic nerve heads and aberrant vascular arrangement.

ATHYROTIC HYPOTHYROIDISM ANOMALAD

(Hypothyroidism Anomalad)

Primary Defect—in Development of Thyroid Gland

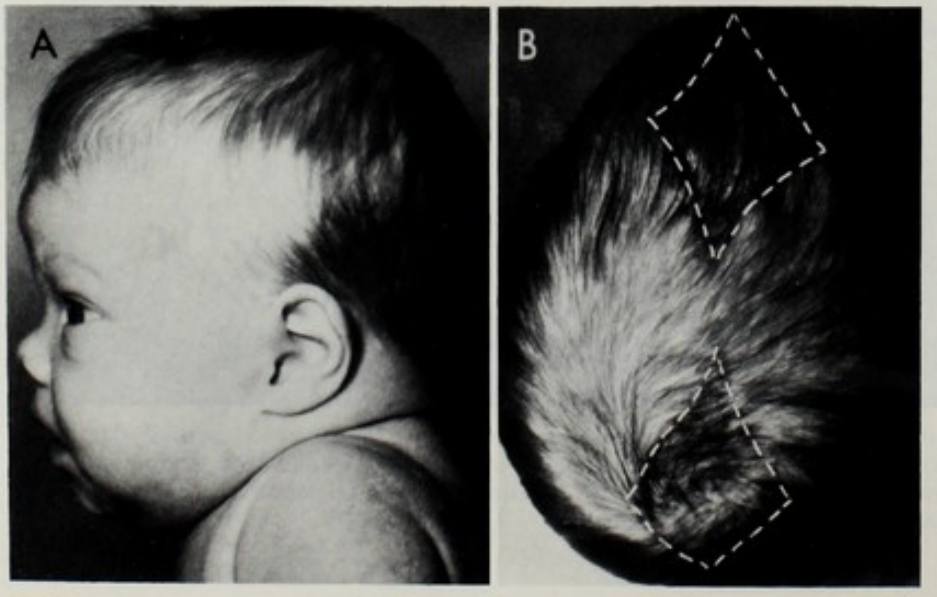
Athyrotic hypothyroidism is usually a sporadic occurrence in an otherwise normal child. Severe hypothyroidism does not give rise to growth deficiency until after birth. Postnatally, morphogenesis and function are grossly impaired as a metabolic consequence of the lack of thyroid hormone. Adequate thyroid hormone replacement therapy, at least ¾ grain of U.S.P. desiccated thyroid for the affected infant, will allow for a complete return to physical normality for age. However, the detrimental effect of the hypothyroid state on morphogenesis and function of the brain is irreparable. Therefore the earlier a diagnosis is made and adequate thyroid hormone therapy instituted, the better is the prognosis for mental function.

ABNORMALITIES. The following are some of the early signs which may allow for detection of the hypothyroid baby early in life. There is usually prenatal onset of osseous immaturity, as evidenced by large fontanels and immature facial bone structure (see below). Myxedema gives rise to full subcutaneous tissues—most evident in the lower eyelids—with enlarged muscle mass and hoarse cry. Klein[3] summarized the relative frequency of signs and symptoms which had been noted prior to three months of age in 31 patients with congenital hypothyroidism.

General	
Feeding problems	39%
Decreased activity	39%
Constipation	52%
Neonatal jaundice	16%
Cutaneous-Vascular	
Cold to touch	19%
Dry skin	45%
Mottling	58%
Myxedema	
Enlarged tongue	45%
Hoarse cry	39%
Other	
Umbilical hernia	58%

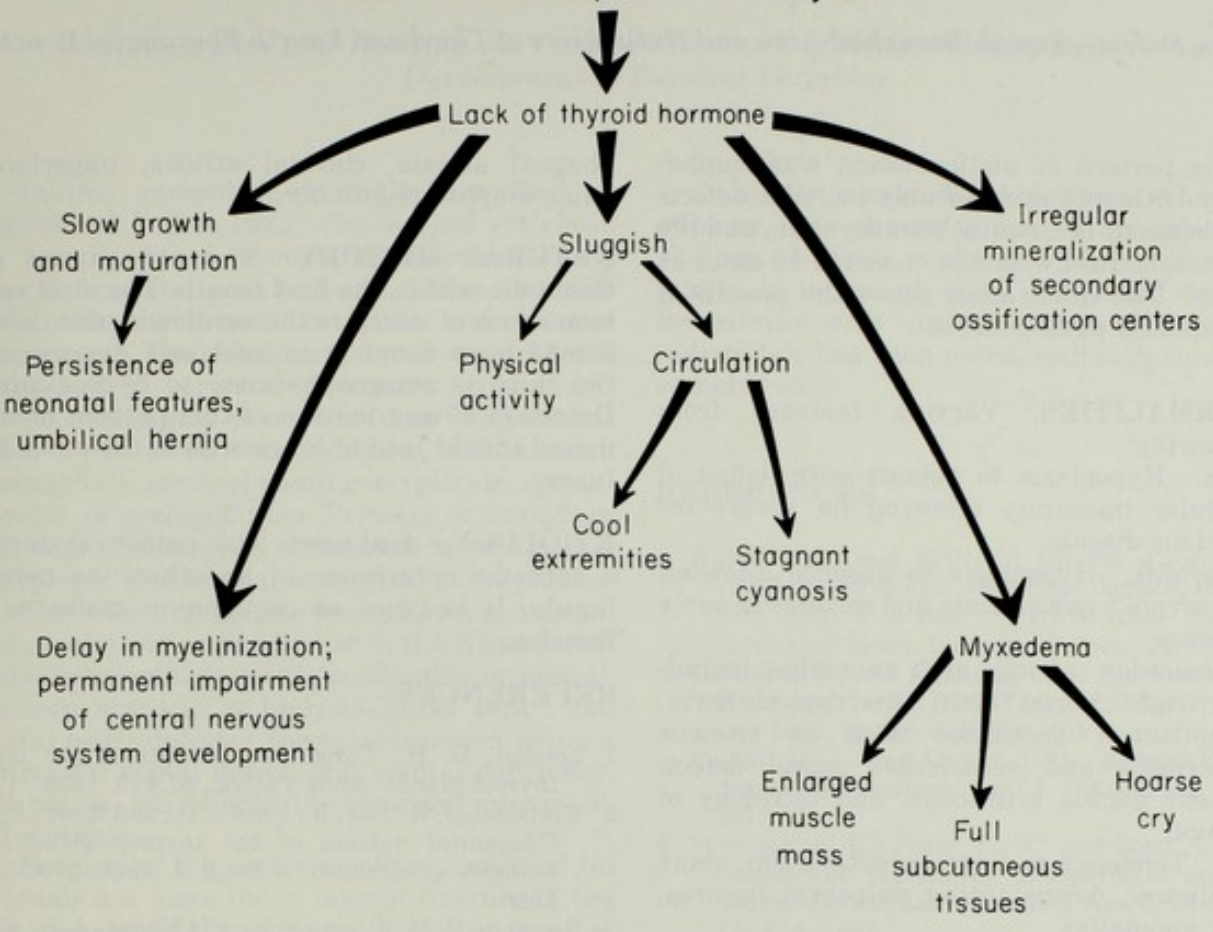
REFERENCES

1. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield, Ill., Charles C Thomas, 1965.
2. Smith, D. W., and Popich, G.: Large fontanels in congenital hypothyroidism. J. Pediatr., *80*:753, 1972.
3. Klein, A. H., Pittsburgh. Personal communication.

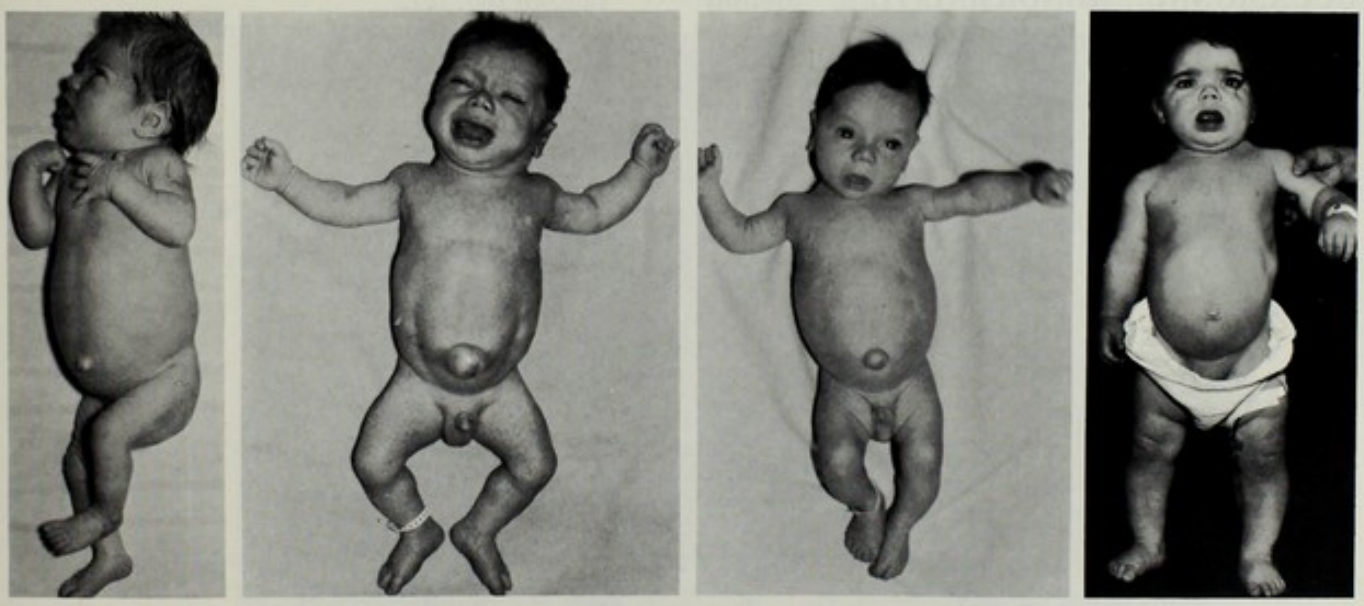


Evidence of osseous immaturity in a 3 month old infant with athyrotic hypothyroidism. *A*, Immature facies with low nasal bridge. Note also the full subcutaneous tissues. *B*, Immaturity of osseous calvarium with outer limits of large fontanels is indicated. The bone age as determined from roentgenograms of the knee and foot was interpreted as being at about an 8 month fetal level.

ATHYROTIC HYPOTHYROIDISM
Defect in Development of Thyroid



Athyrotic Patients



Age - 2 months
Height age - 1 mo.
Bone age - birth

Age - 9 months
Height age - 2 months
Bone age - birth

→

After 3 weeks of thyroid replacement

Age - 3 years, untreated
Height age - 12 mo.
Bone age - 3 months

DiGEORGE ANOMALAD

Primary Defect—Fourth Branchial Arch and Derivatives of Third and Fourth Pharyngeal Pouches

This pattern of malformation was emphasized by DiGeorge and variably includes defects of development of thymus, parathyroids, and the great vessels. Beckwith has observed 19 cases at necropsy.[4] The illustration shows the presumed developmental pathogenesis.

ABNORMALITIES. Varying features from the following:

Thymus. Hypoplasia to aplasia with deficit of cellular immunity allowing for severe infectious disease.

Parathyroids. Hypoplasia to absence allowing for severe hypocalcemia and seizures in early infancy.

Cardiovascular. Aortic arch anomalies including right aortic arch, interrupted aorta, conotruncal anomalies such as truncus arteriosus and ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot.

Facial. Tendency to have hypertelorism, short philtrum, downslanting palpebral fissures, ear anomalies.

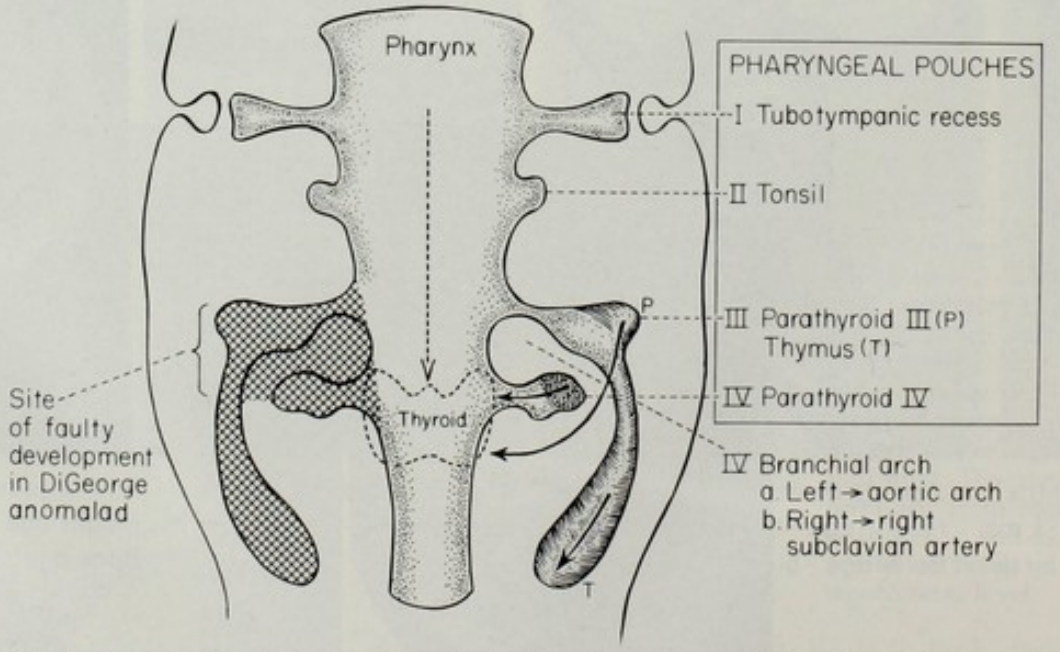
OCCASIONAL ABNORMALITIES. Mental deficiency of mild to moderate degree. Esophageal atresia, choanal atresia, imperforate anus, diaphragmatic hernia.

NATURAL HISTORY. The majority of patients die within the first month. The most common cause of death is the cardiovascular defect, second most common is infectious disease, and the third is seizures relative to hypocalcemia. Detection of any feature of this pattern of anomalad should lead to concern as to the other features.

ETIOLOGY. Unknown. This pattern is usually a sporadic occurrence in an otherwise normal family. It is twice as common in males as in females.

REFERENCES

1. Lobdell, D. H.: Congenital absence of the parathyroid glands. Arch. Pathol., *67*:412, 1959.
2. Kretschmer, R., Say, B., Brown, D., and Rosen, F. S.: Congenital aplasia of the thymus gland (DiGeorge's syndrome). N. Engl. J. Med., *279*:1295, 1968.
3. Freedom, R. M., Rosen, F. S., and Nadas, A. S.: Congenital cardiovascular disease and anomalies of the third and fourth pharyngeal pouch. Circulation, *46*:165, 1972.
4. Beckwith, J. B.: Personal communication.



Schematic appearance of anterior foregut and its derivatives at around the fifth week of development, showing the presumed site of defect of the DiGeorge anomaly.

KLIPPEL-FEIL ANOMALAD

Short Neck with Low Hairline and Limited Movement of Head; Primary Defect—Early Development of Cervical Vertebrae

In this anomalad, originally described by Klippel and Feil in 1912,[1] the cervical vertebrae are usually fused, though hemivertebrae and other defects may also be found. There may also be secondary web neck, torticollis, and/or facial asymmetry. The frequency is about 1:42,000 births and 65 per cent of patients are female.[2] The anomalad may be a part of a serious problem in early neural tube development such as with iniencephaly, cervical meningomyelocele, syringomyelia, or syringobulbia. Primary or secondary neurologic deficits may occur, such as paraplegia, hemiplegia, and cranial or cervical nerve palsies.

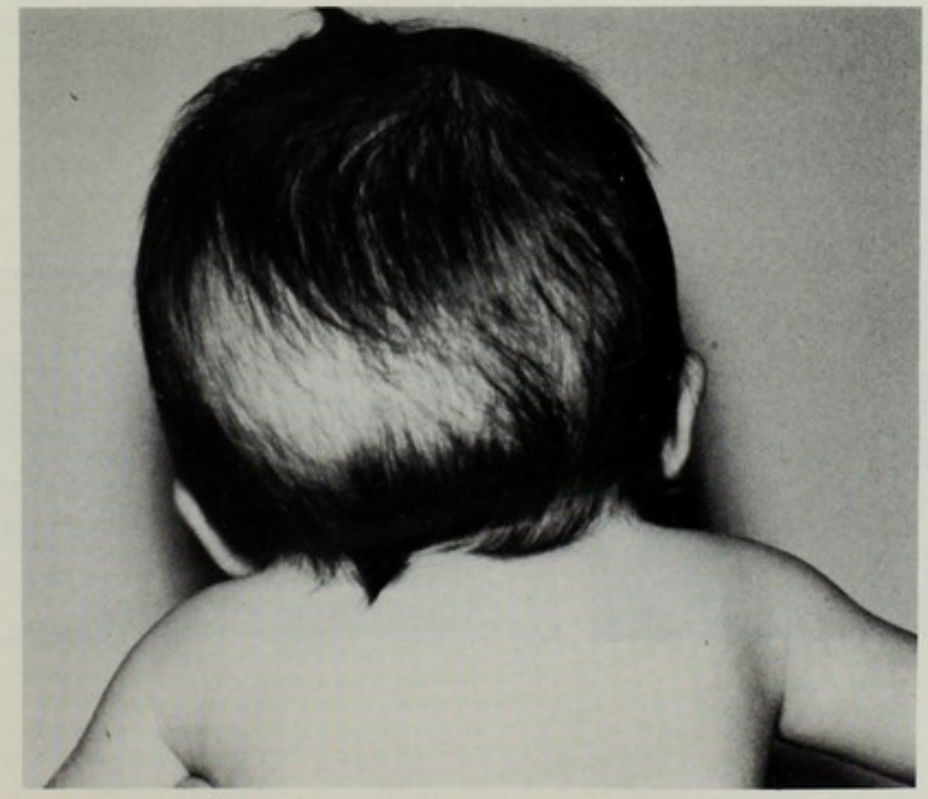
The following defects have shown a nonrandom association in patients with the Klippel-Feil anomalad: deafness, either conductive or neural, has been noted in as high as 30 per cent;[3] congenital heart defects,[4] the most common being a ventricular septal defect; and mental deficiency, cleft palate, rib defects, the Sprengel anomalad, and scoliosis.

Because of the neck immobility, affected individuals are more liable toward fracture of the neck and should therefore avoid violent trauma.

Usually a sporadic occurrence of unknown etiology, this anomalad has rarely occurred in siblings. A close evaluation of the immediate family is indicated, since autosomal dominant inheritance with variable expression in affected individuals has been noted, although this is presumably rare.

REFERENCES

1. Klippel, M., and Feil, A.: Un cas d'absence des vertébres cervicales, avec cage thoracique remontant jusqu'à la base du crâne (cage thoracique cervicale). Mouv. Inconogr. Salpêt., *25*:223, 1912.
2. Gorlin, R. J., and Pindborg, J. J.: Syndromes of the Head and Neck. New York, McGraw-Hill Book Co., 1963, pp. 99, 335–338, 401.
3. Palant, D. J., and Carter, B. L.: Klippel-Feil syndrome and deafness. Am. J. Dis. Child., *123*:218, 1972.
4. Morrison, S. G., Perry, L. W., and Scott, L. P., III: Congenital brevicollis (Klippel-Feil syndrome) and cardiovascular anomalies. Am. J. Dis. Child., *115*:614, 1968.



Infant with the Klippel-Feil anomalad.

ABDOMINAL MUSCLE DEFICIENCY ANOMALAD

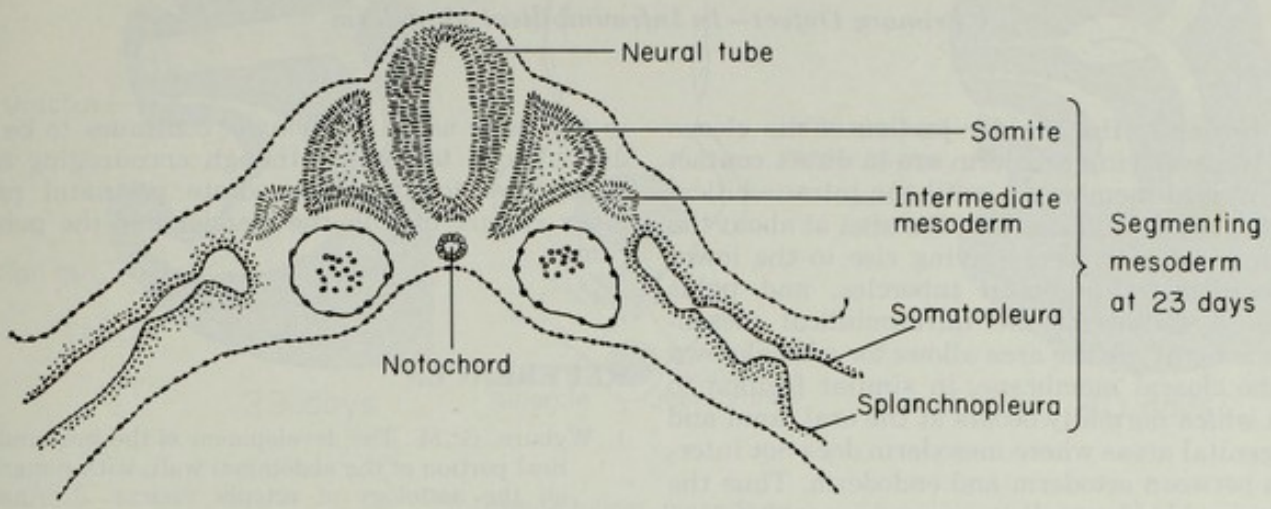
Abdominal Muscle Hypoplasia, Urinary Tract Dysplasia, Cryptorchidism; Primary Defect—Early Mesodermal Defect

The remarkable similarity among affected individuals with abdominal muscle deficiency suggests that this "disorder" may be the consequence of a single localized defect in early mesoderm which eventually contributes to the formation of the abdominal musculature, the urinary tract musculature, the renal parenchyma, and possibly the gubernaculum testis. The condition occurs predominantly in males who occasionally have defects of the lower limbs as well. The incidence is about one in 50,000. The prognosis for these patients is mainly dependent on the degree of renal insufficiency and complications arising from poor drainage of the urinary tract. Abdominal binding will often improve respiratory exchange and assist in the patient's having bowel movements. Some improvement in abdominal muscle mass and function may occur with age. Because these patients are usually of normal intelligence all supportive measures seem indicated.

REFERENCES

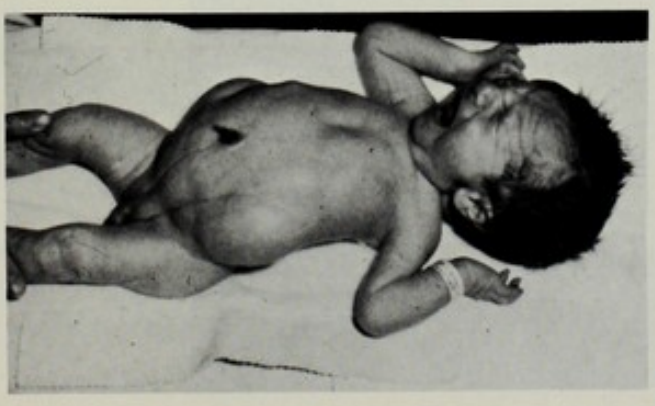
1. Parker, R. W.: Case of an infant in whom some of the abdominal muscles were absent. Clin. Soc. Trans., *28*:201, 1895.
2. Silverman, F. N., and Huang, N.: Congenital absence of the abdominal muscles. Am. J. Dis. Child., *80*:91, 1950.
3. Lattimer, J. K.: Congenital deficiency of abdominal musculature and associated genitourinary anomalies. J. Urol., *79*:343, 1958.
4. Miller, R. M., Kind, R. E., and Rich, R. W.: Congenital anomalies of the abdominal musculature and urogenital tract in a foal. Vet. Med., *61*:652, 1966.

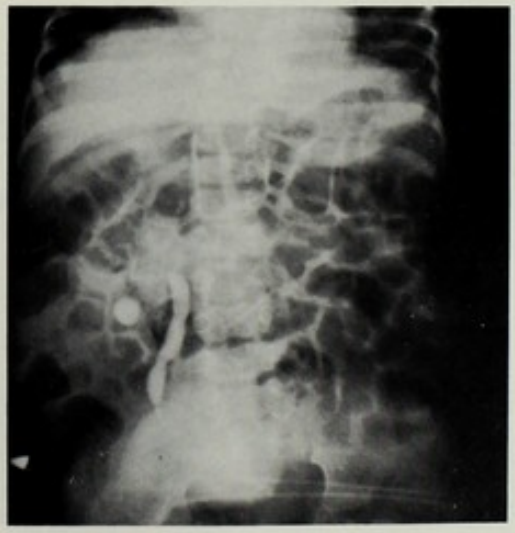
Abdominal Muscle Deficiency, Renal and Urinary Tract Anomalies, and Cryptorchidism



EARLY DEFECT IN MESODERM CONTRIBUTING TO

- Somite → Myotome → Abdominal muscle agenesis to hypoplasia
- Intermediate mesoderm → Renal parenchyma → Hypoplasia and/or dysgenesis of kidney
- Splanchnopleura → Musculature of ureter, bladder → Abnormal hyaloid wall of ureter and bladder, cryptorchidism





EXSTROPHY OF BLADDER ANOMALAD

Primary Defect—In Infraumbilical Mesoderm

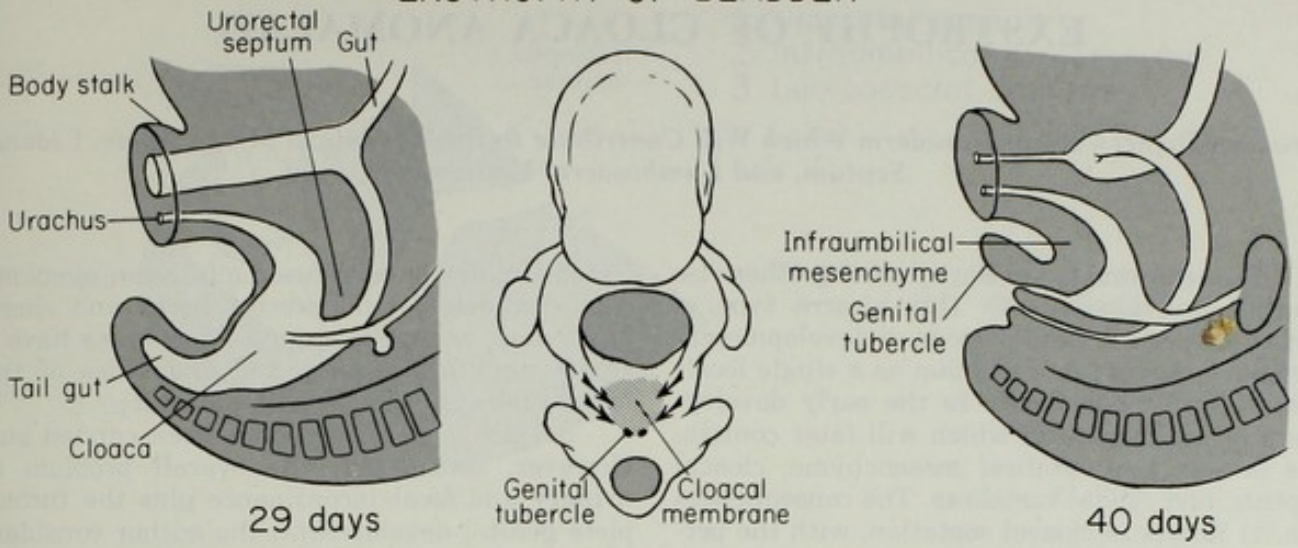
Normally the bladder portion of the cloaca and the overlying ectoderm are in direct contact (the cloacal membrane) until the infraumbilical mesenchyme migrates into the area at about the sixth to seventh week, giving rise to the lower abdominal wall, genital tubercles, and pubic rami. A failure of the infraumbilical mesenchyme to invade the area allows for a breakdown in the cloacal membrane, in similar fashion to that which normally occurs at the oral, anal and urogenital areas where mesoderm does not intercede between ectoderm and endoderm. Thus the posterior bladder wall is exposed in conjunction with defects in structures derived from the infraumbilical mesenchyme.

This anomalad, six times as likely to occur in the male as in the female, continues to be a difficult one to correct, though encouraging results have followed immediate postnatal primary closure of both the bladder and the pubic rami.

REFERENCES

1. Wyburn, G. M.: The development of the infraumbilical portion of the abdominal wall, with remarks on the aetiology of ectopia vesicae. J. Anat., *71*:201, 1937.
2. Muecke, E. C.: The role of the cloacal membrane in exstrophy: the first successful experimental study. J. Urol., *92*:659, 1964.

EXSTROPHY OF BLADDER



Infraumbilical mesoderm
fills in all of cloacal membrane
except urogenital floor.
Genital tubercles fuse

↓

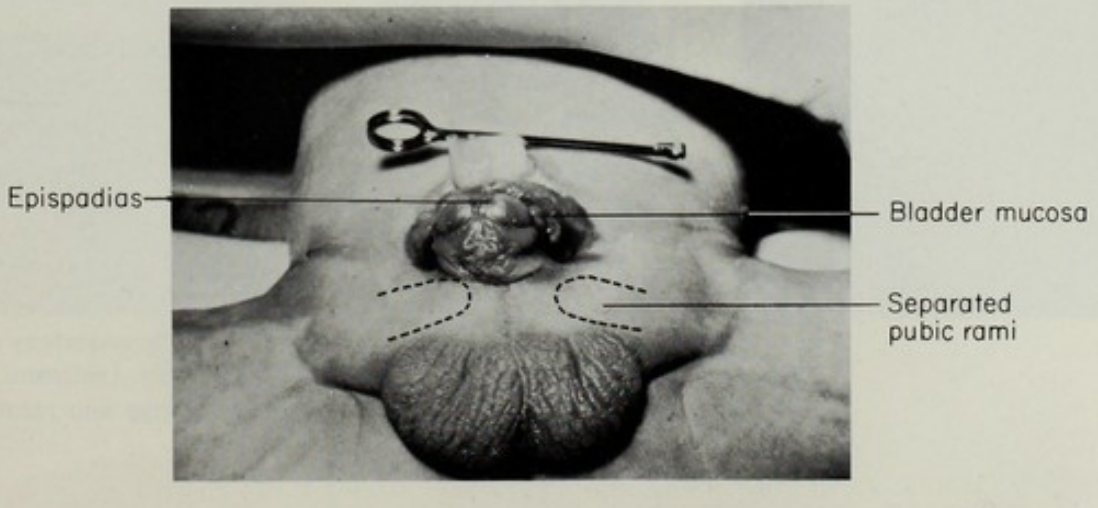
Failure of
infraumbilical mesoderm
to invade cloacal membrane

↙ ↓ ↘

Breakdown of cloacal membrane exposing posterior wall of bladder

Incomplete fusion of genital tubercles, often with epispadias

Separated pubic rami, short lower abdominal wall, +/- inguinal herniae



EXSTROPHY OF CLOACA ANOMALAD

Primary Defect—Early Mesoderm Which Will Contribute to Infraumbilical Mesenchyme, Cloacal Septum, and Lumbosacral Vertebrae

The remarkable similarity among otherwise normal individuals with this bizarre type of defect suggests a similar mode of developmental pathology having its inception as a single localized defect—theoretically in the early development of the mesoderm which will later contribute to the infraumbilical mesenchyme, cloacal septum, and caudal vertebrae. The consequences are (1) failure of cloacal septation, with the persistence of a common cloaca into which the ureters, ileum, and a rudimentary hindgut open; (2) complete breakdown of the cloacal membrane with exstrophy of the cloaca, failure of fusion of the genital tubercles and pubic rami, and often an omphalocele; and (3) incomplete development of the lumbosacral vertebrae with herniation of a grossly dilated central canal of the spinal cord (hydromyelia), yielding a soft, cystic, skin-covered mass over the sacral area—sometimes asymmetric in its positioning. The rudimentary hindgut may contain two appendices, and there is no anal opening. The small intestine may be relatively short. Cryptorchidism is a usual finding in the male. Affected females have unfused müllerian elements with completely bifid uterine horns and short, duplicated, or atretic vagina. Most cases have a single umbilical artery, and anomalies of the lower limbs are occasionally present.

Surgical intervention has been carried out. However, considering the overall problem of urinary and fecal incontinence plus the incomplete genital development, the author considers that a decision toward surgical partial correction should be undertaken only after careful consideration with the family.

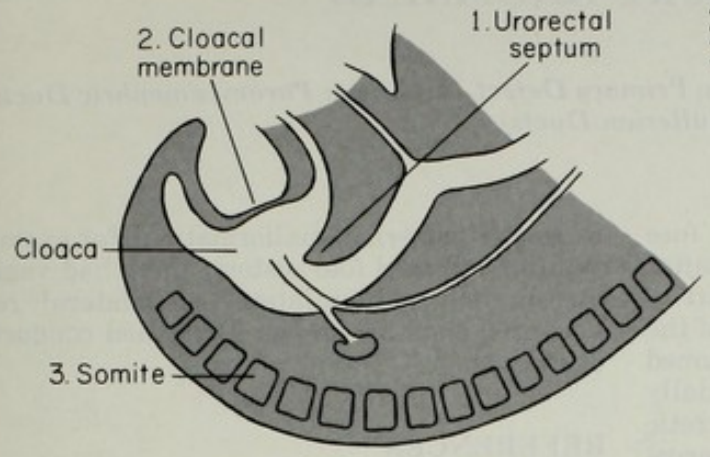
REFERENCES

1. Beckwith, J. B.: The congenitally malformed. VII. Exstrophy of the bladder and cloacal exstrophy. Northwest Med., *65*:407, 1966.
2. Zwiren, G. T., and Patterson, J. H.: Exstrophy of the cloaca: report of a case treated surgically. Pediatrics, *35*:687, 1965.
3. Spencer, R.: Exstrophia splanchnica (exstrophy of the cloaca). Surgery, *57*:751, 1965.

EXSTROPHY OF CLOACA

Defect in early mesoderm which will contribute to:

1. Urorectal septum
2. Infraumbilical mesenchyme
3. Lumbosacral somites

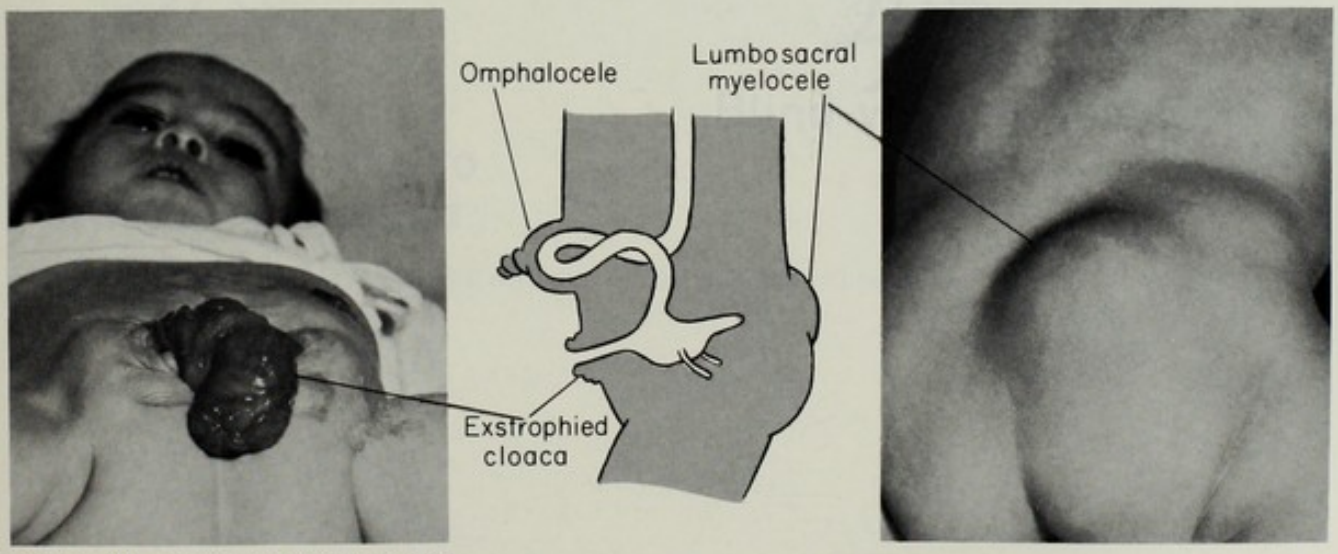


29 DAYS

1.
FAILURE OF CLOACAL SEPTATION
↓
Persistant cloaca
↓
Rudimentary hindgut with imperforate anus

2.
BREAKDOWN OF CLOACAL MEMBRANE
↓
Exstrophy of cloaca
Failure of fusion of genital tubercles and pubic rami
↓
+/- Omphalocele

3.
LUMBOSACRAL SPINA BIFIDA
↓
Protrusion of dilated central canal of spinal cord: HYDROMYELIA



Infant with exstrophy of the cloaca (prolapsed intestine). Note separation of scrotal folds and genital tubercle.

ROKITANSKY ANOMALAD

Vaginal Atresia and Rudimentary Uterus; Primary Defect—In Lower Paramesonephric Ducts (Müllerian Ducts)

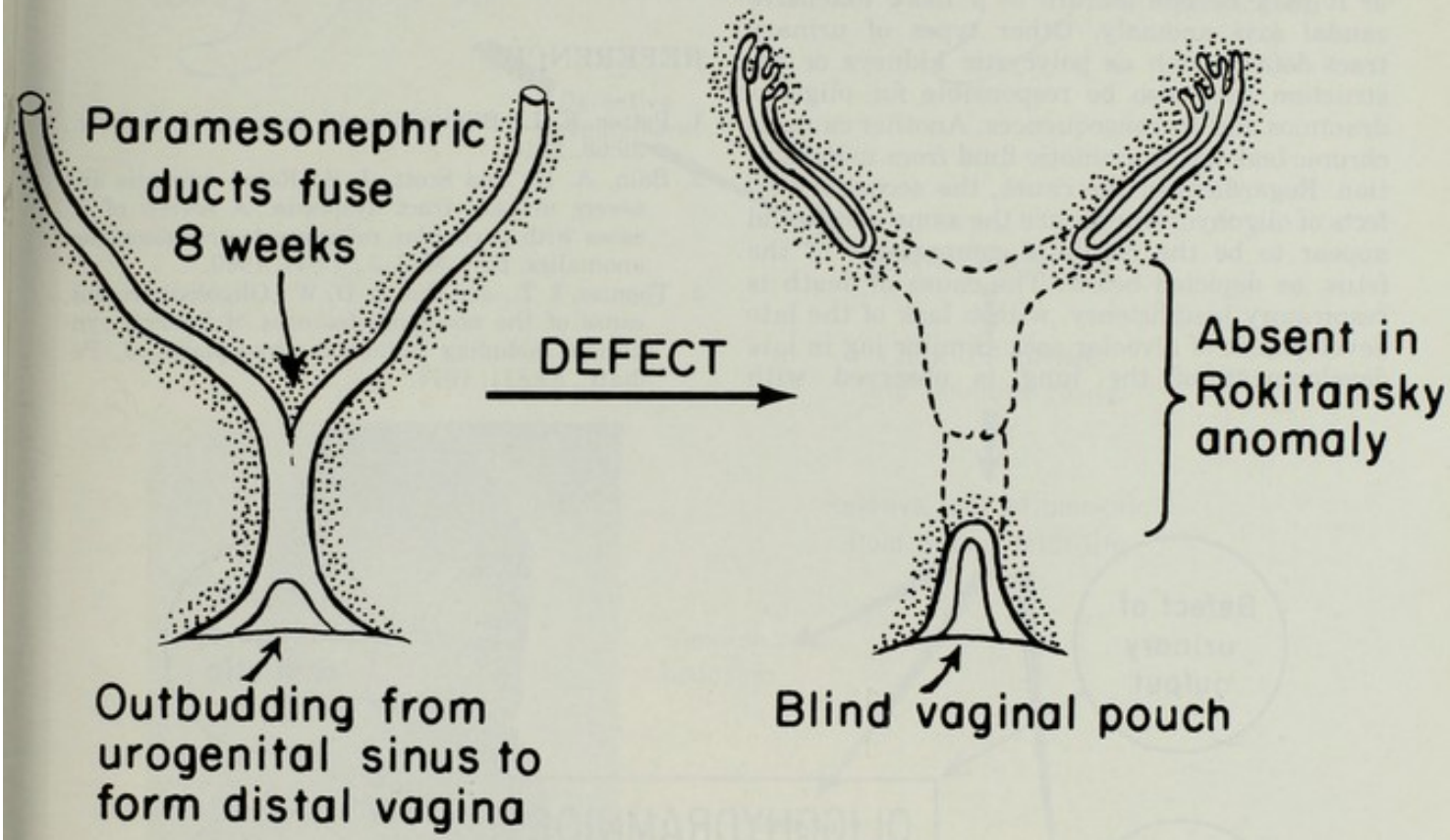
The paramesonephric ducts normally fuse caudally at about eight weeks and thereafter form the uterus, cervix, and the upper part of the vagina. A single defect in development of the caudal paramesonephric ducts is the presumed explanation for the pattern of anomaly initially reported by Rokitansky: incomplete to atretic vagina and rudimentary to bicornuate uterus. The Fallopian tubes and ovaries are usually near-normal with normal secondary sexual characteristics, save for a lack of menstruation. The lower vagina, which derives as an outpouching from the urogenital sinus, is usually present as a blindly ending pouch. The cause is unknown, with most cases being sporadic. About 4 per cent of cases have been familial, with affected female siblings.

Associated anomalies include defects in other derivatives of the mesonephric ridge. About one third to one half of cases have a renal anomaly such as renal agenesis, hypoplasia, or double ureters. Also about 10 per cent of cases have a vertebral and/or rib anomaly.

The Rokitansky anomalad may be a part of a broader pattern of malformation. For example, Winter[5] reported four sisters; three had vaginal atresia, all had unilateral or bilateral renal agenesis, and the two survivors had conductive deafness.

REFERENCES

1. Rokitansky, K.: Übr sog. Verdoppelung des Uterus. Med. Jahrb. des Osterreich. Staates, *26*:39, 1838.
2. Bryan, A. L., Nigro, J. A., and Counseller, V. S.: One hundred cases of congenital absence of the vagina. Surg. Gynecol. Obstet., *88*:79, 1949.
3. Leduc, B., Van Campenjout, J., and Simard, R.: Congenital absence of the vagina. Observations on 25 cases. Am. J. Obstet. Gynecol., *100*:512, 1968.
4. Anger, D., Hemet, J., and Ensel, J.: Forme familiale du syndrome de Rokitansky-Kuster-Hauser. Bull. Fed. Soc Gynecol. Obstet. Lang. Fr., *18*:229, 1966.
5. Winter, J. S. D., Kohn, G., Mellman, W. J., and Wagner, S.: A familial syndrome of renal, genital, and middle ear anomalies. J. Pediatr., *72*:88, 1968.



Presumed derivation of the Rokitansky anomalad.

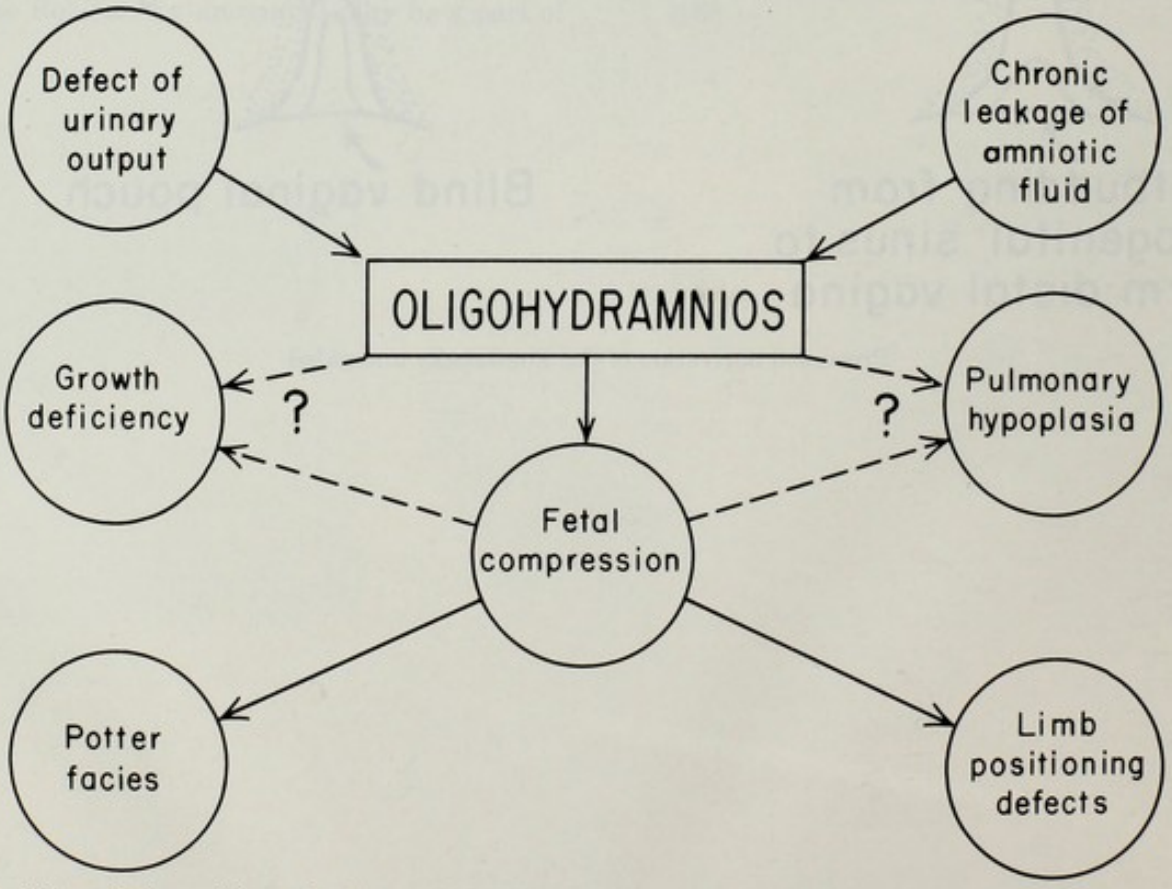
OLIGOHYDRAMNIOS TETRAD
(Potter Syndrome)

Primary Defect—Development of Oligohydramnios

Renal agenesis, which must have occurred prior to 31 days, will secondarily limit the amount of amniotic fluid and thereby result in further anomalies during prenatal life. The renal agenesis may be the only primary defect, or it may be one feature of a more extensive caudal axis anomaly. Other types of urinary tract defects such as polycystic kidneys or obstruction may also be responsible for oligohydramnios and its consequences. Another cause is chronic leakage of amniotic fluid from midgestation. Regardless of the cause, the secondary effects of oligohydramnios are the same and would appear to be the result of compression of the fetus, as depicted below. The cause of death is respiratory insufficiency, with a lack of the late development of alveolar sacs. Similar lag in late development of the lung is observed with diaphragmatic hernia or asphyxiating thoracic dystrophy. In both of these latter situations there is external compression of developing lung; this is considered the most likely cause in oligohydramnios also, as shown in the figure.

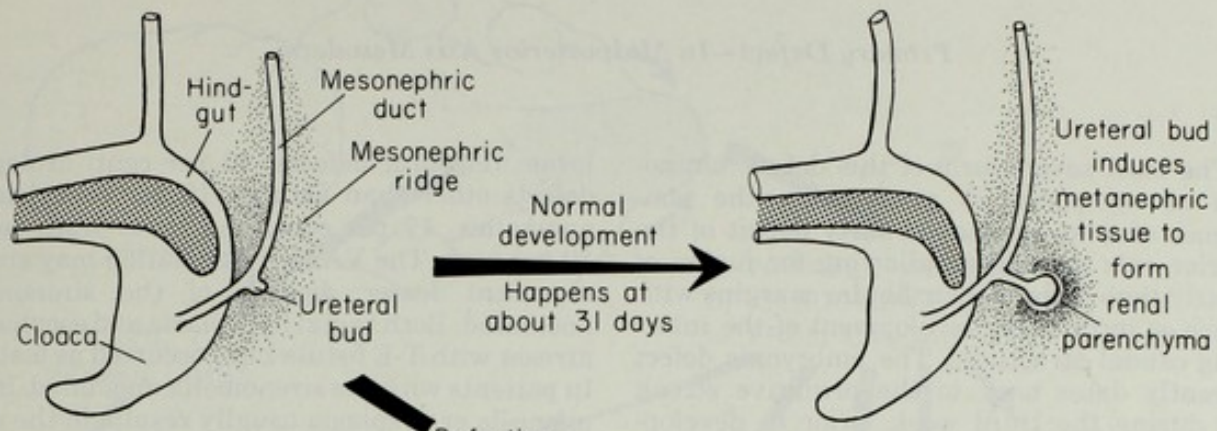
REFERENCES

1. Potter, E. L.: Bilateral renal agenesis. J. Pediatr., *29*:68, 1946.
2. Bain, A. D., and Scott, J. S.: Renal agenesis and severe urinary tract dysplasia. A review of 50 cases with particular reference to the associated anomalies. Brit. Med. J., *1*:841, 1960.
3. Thomas, I. T., and Smith, D. W.: Oligohydramnios, cause of the non-renal features of Potter's syndrome, including pulmonary hypoplasia. J. Pediatr., *84*:811, 1974.



Depiction of the origin and effects of oligohydramnios. The "oligohydramnios tetrad" is implied to be secondary to fetal compression.

The Consequences of Renal Agenesis



Defective development

RENAL AGENESIS

LACK OF URINE into amniotic cavity

Relative lack of amniotic fluid during fetal life



Amnion nodosum

Pulmonary hypoplasia

Death from respiratory insufficiency

Fetal compression

Altered facies

Abnormal positioning hands and feet

Breech presentation

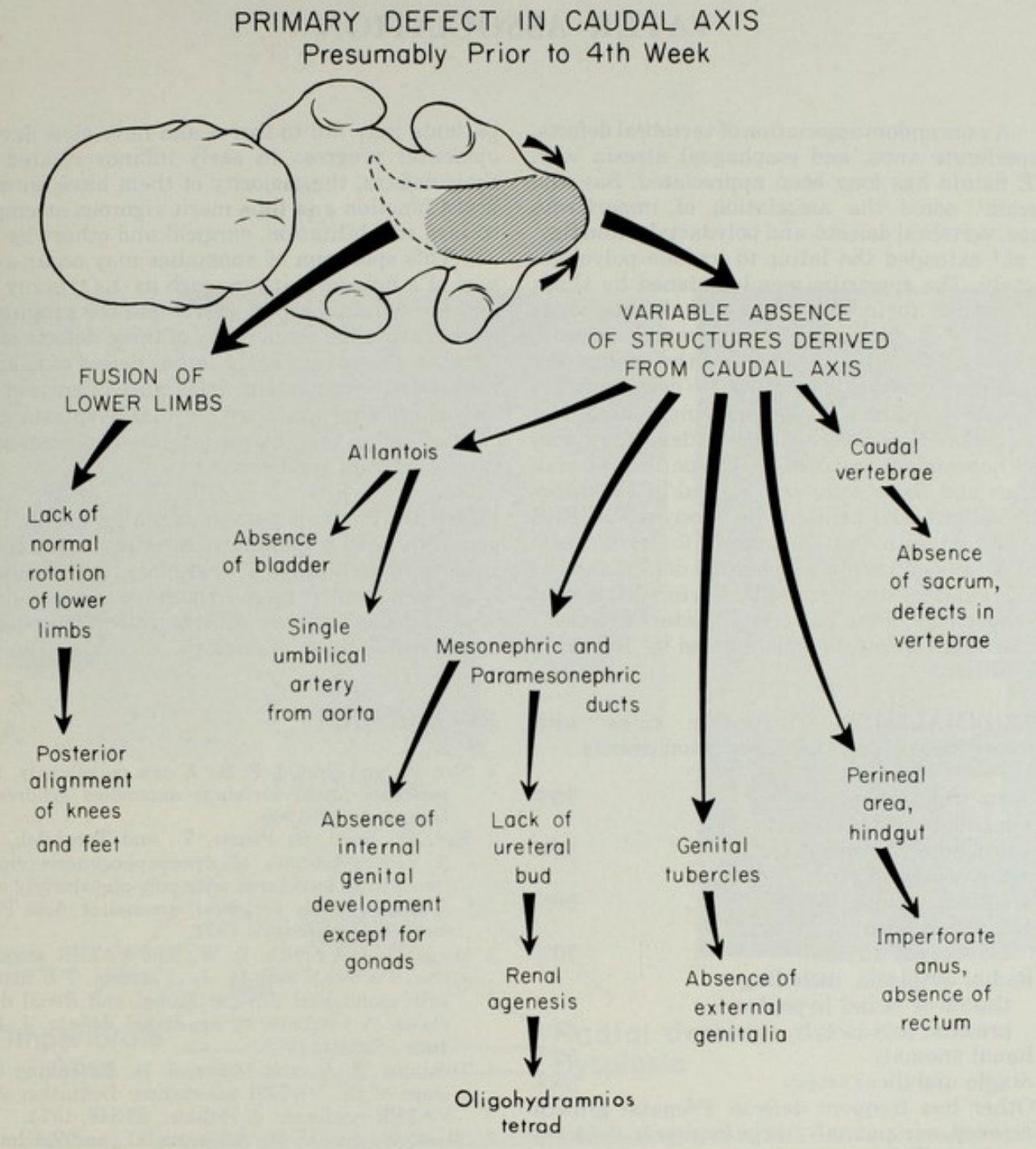
SIRENOMELIA (MERMAID) ANOMALAD
(Caudal Regression Anomalad)

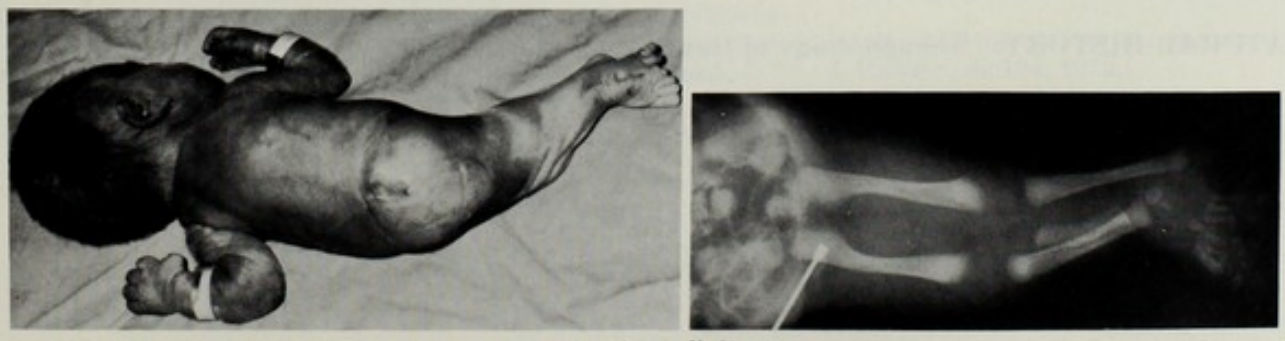
Primary Defect—In Midposterior Axis Mesoderm

The most severe form of this defect, sirenomelia or sympodia, is presumably the consequence of a wedge-shaped early deficit of the posterior axis mesoderm; allowing for fusion of the early limb buds at their fibular margins with absence or incomplete development of the intervening caudal structures. The embryonic defect apparently dates back to the primitive streak stage during the third week, prior to development of the allantois, for there is usually an absence of allantoic vessels. The single umbilical artery arises directly from the aorta, rather than the usual two umbilical arteries arising from the hypogastric vessels. This defect, occurring in about one in 60,000 newborns, has a 2.7:1 male sex preponderance. It is more common in one of identical twins. All degrees of severity are observed, presumably dependent on the relative length and width of the early caudal deficit. The variable consequences are often called the caudal regression syndrome. Conceivably, imperforate anus might represent a minor degree of this type of defect. It is important to appreciate that the following defects of the caudal axis may be present in an individual with imperforate anus: lower vertebral defects, 40 per cent; urological defects other than fistulas, 19 per cent; genital anomalies, 17 per cent; and lower limb defect, 10 per cent. The VATER association may simply represent lesser degrees of the sirenomelia anomalad. Both radial hypoplasia and esophageal atresia with T-E fistula have occurred as features in patients with the sirenomelia anomalad. Renal agenesis or dysplasia usually results in the additional findings of the oligohydramnios tetrad.

REFERENCES

1. Wolff, E.: Les bases de la tératogénèse expérimentale des vértebrés amniotes, d'après les résultats de méthodes directes. Arch. Anat. Histol. Embryol. (Strasb.), *22*:1, 1936.
2. Duhamel, B.: From the mermaid to anal imperforation: the syndrome of caudal regression. Arch. Dis. Child., *36*:152, 1961.
3. Crawfurd, M. d'A., Ismail, S. R., and Wigglesworth, J. S.: A monopodal sireniform monster with dermatoglyphic and cytogenetic studies. J. Med. Genet., *3*:212, 1966.





Newborn with sirenomelia, a severe caudal axis deficit

VATER ASSOCIATION

A nonrandom association of vertebral defects, imperforate anus, and esophageal atresia with T-E fistula has long been appreciated. Say and Gerald[1] noted the association of imperforate anus, vertebral defects, and polydactyly, and Say, et al.[2] extended the latter to include polyoligodactyly. The spectrum was broadened by Quan and Smith[3] to include *V*ertebral defects, *A*nal atresia, *T-E* fistula with esophageal atresia, *R*adial and *R*enal dysplasia, and the acronym of VATER association was utilized to designate this complex. Cardiac defects and single umbilical artery as well as prenatal growth deficiency were also nonrandom features of this pattern of anomalies and these were emphasized by Temtamy and Miller,[4] who utilized the eponym VATERS association with the *V* standing for both vertebral defects and ventricular septal defect, and the *S* designating single umbilical artery. The general spectrum of the pattern in a total of 34 cases is presented below, as summarized by Temtamy and Miller.[4]

ABNORMALITIES. Thirty-four cases with three or more of VATER association defects.

Vertebral anomalies	70%
Ventricular septal defects and other cardiac defects	53%
Anal atresia with or without fistula	80%
T-E fistula with esophageal atresia	70%
Radial dysplasia, including thumb or radial hypoplasia, preaxial polydactyly, syndactyly	65%
Renal anomaly	53%
Single umbilical artery	35%

Other less frequent defects: Prenatal growth deficiency, ear anomaly, large fontanels, defect of lower limb (23%), and rib anomaly.

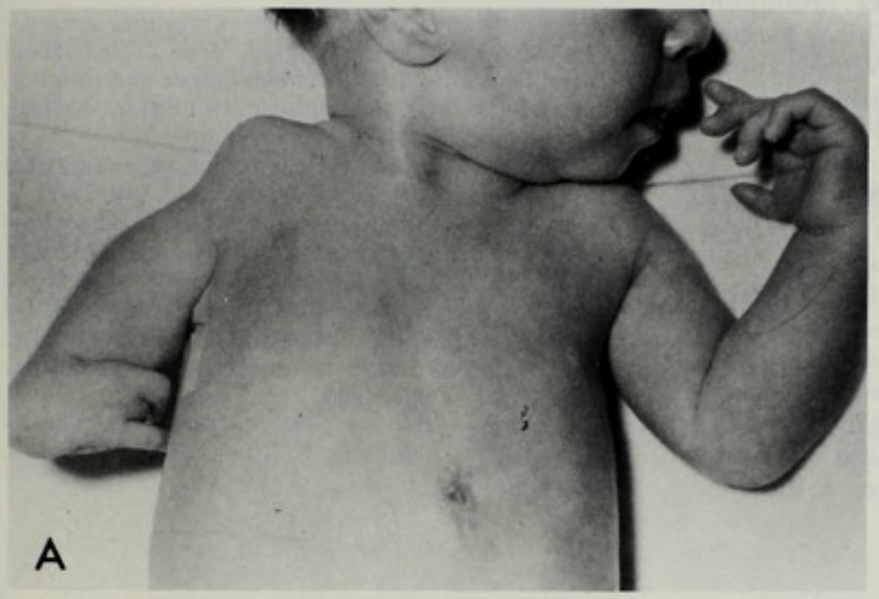
NATURAL HISTORY. Though many of these patients may fail to thrive and have slow developmental progress in early infancy related to their defects, the majority of them have normal brain function and thus merit vigorous attempts toward rehabilitation, surgical and otherwise.

This spectrum of anomalies may occur as a part of a broader pattern, such as the trisomy 18 or 13q− syndromes, in which case the prognosis is not favorable. Also, many of these defects may occur in the severe early lethal defect of caudal mesoderm, sirenomelia. It is also important to appreciate that cases with radial dysplasia and cardiac defect may be mistakenly designated as the Holt-Oram syndrome.[5]

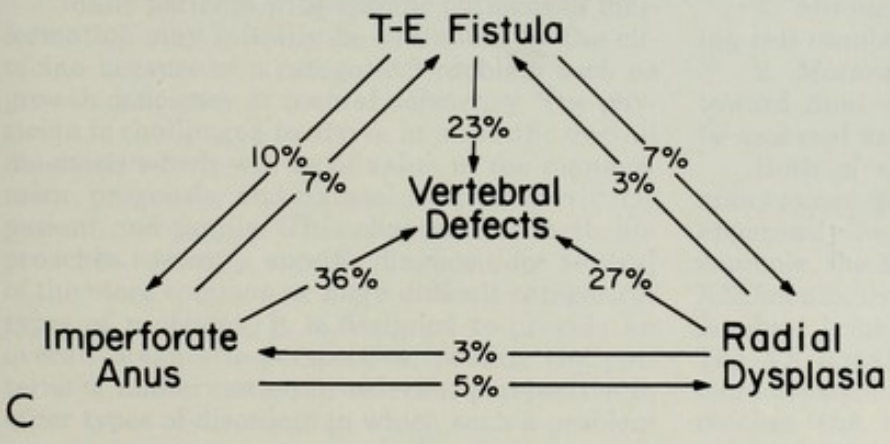
ETIOLOGY. This pattern of malformation has generally been a sporadic occurrence in an otherwise normal family. The etiology is unknown. Quan and Smith[3] have hypothesized a common type of defect in early differentiating mesoderm as a possible mode of etiology.

REFERENCES

1. Say, B., and Gerald, P. S.: A new polydactyly, imperforate anus, vertebral anomalies syndrome. Lancet, *2*:688, 1968.
2. Say, D., Balci, S., Pirnar, T., and Tuncbilek, E.: A new syndrome of dysmorphogenesis-imperforate anus associated with poly-oligodactyly and skeletal (mainly vertebral) anomalies. Acta Paediatr. Scand., *60*:197, 1971.
3. Quan, L., and Smith, D. W.: The VATER association, *V*ertebral defects, *A*nal atresia, *T-E* fistula with esophageal atresia, *R*adial and *R*enal dysplasia: A spectrum of associated defects. J. Pediatr., *82*:104, 1973.
4. Temtamy, S. A., and Miller, J. D.: Extending the scope of the VATER association: Definition of a VATER syndrome. J. Pediatr., *85*:345, 1974.
5. Silver, W., Steier, M., Schwartz, O., and Zeichner, M. B.: The Holt-Oram syndrome with previously undescribed associated anomalies. Am. J. Dis. Child., *124*:911, 1972.







A, Young infant with vertebral anomalies, anal atresia, esophageal atresia with T-E fistula, radial aplasia on the right, and thumb hypoplasia on the left.

B, Same patient at two years of age, with normal intelligence.

C, Relative frequencies of some of the other VATER association defects when the patient is ascertained by virtue of having one of the defects. (From Quan, L., and Smith, D. W.: J. Pediatr., *82*:104, 1973.)

WILMS' TUMOR ASSOCIATIONS

1. ANIRIDIA-WILMS' TUMOR ASSOCIATION.[1–4] At least 30 cases of the association of Wilms' tumor and aniridia have been reported and it is estimated that one in 70 patients with aniridia also has Wilms' tumor. Many of these patients also have other defects including cataract, microcephaly, mental deficiency, prominent ears, and genitourinary anomaly. This is usually a sporadic occurrence in a family; Wilms' tumor has not been noted in association with autosomal dominant aniridia.

2. HEMIHYPERTROPHY-WILMS' TUMOR ASSOCIATION.[5,6] About one in 30 patients with Wilms' tumor has hemihypertrophy, although the reverse incidence is not known. Other serious tumors less commonly associated with hemihypertrophy include adrenocortical tumor and hepatoblastoma. Possibly some of the cases of association between hemihypertrophy and these tumors represent unrecognized instances of Beckwith-Wiedemann syndrome, a disorder in which both hemihypertrophy (14 per cent) and one of the above mentioned intraabdominal tumors (6 per cent) are liable to be features.

REFERENCES

1. Miller, R. W.: Relation between cancer and congenital defects in man. N. Engl. J. Med., *275*:87, 1966.
2. Miller, R. W.: Relation between cancer and congenital defects: An epidemiologic evaluation. J. Natl. Cancer Inst., *40*:1079, 1968.
3. Balci, S., and Say, B.: Wilm's tumor and congenital malformations. Turk. J. Pediatr., *11*:146, 1969.
4. Neidhart, M.: Wilms-Tumor und Aniridie-ein genetisch fixiertes Syndrom. Klin. Paediatr., *184*:312, 1972.
5. Fraumeni, J. F., Geiser, C. G., and Manning, M. D.: Wilms' tumor and congenital hemihypertrophy: Report of five new cases and review of literature. Pediatrics, *40*:886, 1967.
6. Wiedemann, H. R.: Exomphalos-Makroglossie-Gigantismus-Syndrom. Z. Kinderheilkd., *115*:193, 1973.

Chapter Two

APPROACHES TO CATEGORICAL PROBLEMS OF

growth deficiency, mental deficiency, arthrogryposis, ambiguous external genitalia

Many patients with specific patterns of malformation may initially be evaluated by the clinician because of a categorical problem such as growth deficiency or mental deficiency. The physician is challenged to arrive at a specific overall diagnosis which will be of value in the management, prognosis, and counsel for that particular patient and family. This chapter sets forth approaches toward a specific diagnosis for several of the more common or more difficult categorical types of problems. It is designed to provide an overall diagnostic perspective, placing the patterns of malformation in relevant perspective to other types of disorders in which such a problem may occur.

Each categorical problem is considered from the standpoint of normal morphogenesis, mechanisms by which abnormal morphogenesis may occur, and the clinical manner of proceeding toward a specific overall diagnosis. These approaches are designed to be rational for the particular problem and germane for the specific patient.

APPROACH TO GROWTH DEFICIENCY

Normal Growth

Assuming proper skeletal organization and ossification, adult stature and the age at which it is achieved are the respective consequences of the following phenomena:

1. *Mitotic* rate and thereby rate of increasing cell number, especially in the epiphyses.
2. *Maturational* rate of the skeletal system toward final epiphyseal ossification, which can be assessed as "bone age."

Both of these processes are influenced by many genes (polygenic). Some of these genes are apparently located in the sex chromosomes. For example, the XY male tends to be taller than the XX female, even in childhood, and the XYY individual is generally taller than the XY male. The XX female matures more rapidly and at a more consistent rate than the XY male and thus reaches the advent of adolescence and final height attainment at an earlier chronologic age than the male.

The genetically determined potential for stature and pace of maturation are dependent upon an adequate supply of certain nutrients, vitamins, hormones, and oxygen to the skeletal cells. The dramatic trend toward increasing size and pace of maturation during the past 100 years is most likely related to better nutrition and relatively less chronic disease during childhood.

Causes of Growth Deficiency

Growth deficiency, although a valuable clinical sign, is a highly nonspecific one. The following are five general categories of growth deficiency, each having somewhat different overall

Table 2.1. Classification of Growth Deficiency

FEATURES	NORMAL VARIANTS	
	Familial Short Stature	*Familial Slow Maturation*
Onset of growth deficiency	Postnatal	Postnatal (early childhood)
Rate of maturation	Normal	Slow
Family history	Short stature	Slow maturation
Final stature	Short	Normal limits
Therapy to increase eventual stature	None	None

FEATURES	ABNORMALS*	
	Primary Skeletal Growth Deficiency	*Secondary Growth Deficiency*
Onset of growth deficiency	Usually prenatal	Usually postnatal
Rate of maturation	Variable, usually normal	Usually retarded
Associated anomalies	Frequent	Unusual, except when causative anomaly
Malproportionment	Frequent	Unusual, except for rickets
General modes of etiology	Chromosomal abnormalities	Environmental
	Mutant gene syndromes, including the osteochondrodysplasias	Defect in nonskeletal organ, including endocrine
	Syndromes of unknown etiology	Metabolic disorders
		Chronic infectious disease
Therapy to increase eventual stature	None at present	Specific treatment can result in "catch-up" growth

*Prenatal infectious disease and Fetal Alcohol syndrome are not included.

characteristics in terms of growth pattern, mode of evaluation toward a specific diagnosis, prognosis for eventual stature, and/or management. The first two categories are variants of normal and the other three represent abnormalities in the growth process. This classification, with the exception of prenatal infectious disease, is summarized in Table 2.1.

Variants of Normal

Familial Short Stature is characterized by an otherwise normal small child who is maturing at a normal rate, as indicated by "bone age," with a family history of small stature in otherwise normal close relatives. Such individuals are usually within normal limits for size at birth, have a consistently slow pace of linear growth during childhood, reach adolescence at a usual age, and are relatively short in final stature.

Familial Slow Maturation is characterized by a slowly maturing child who is short for chronologic age but not for maturational age (bone age), with a family history of slow maturation. The latter is indicated by late advent of adolescence and final height attainment in one or more close relatives. Such individuals are usually within normal limits for size at birth, with slowing in the pace of growth and maturation becoming evident during late infancy or early childhood. They have a late onset of a normal adolescence and usually achieve a final height within the normal range, but at a late chronologic age.

Abnormal Growth

Aside from the rare and rather obvious situation of sexual precocity leading to rapid growth and accelerated maturation with an early and relatively short final height attainment, the other growth deficiency disorders can be grouped into three general categories. The general distinction between the first two is illustrated in Figure 2.1.

Primary Skeletal Growth Deficiency. The implication for this category is that of a primary intracellular problem which affects the growth of the skeletal system. The growth deficiency is usually of prenatal onset and is often accompanied by malproportionment or defects in skeletal molding. The same problem which affects cellular growth and morphogenesis in the skeleton may have affected other tissues as well. Thus the

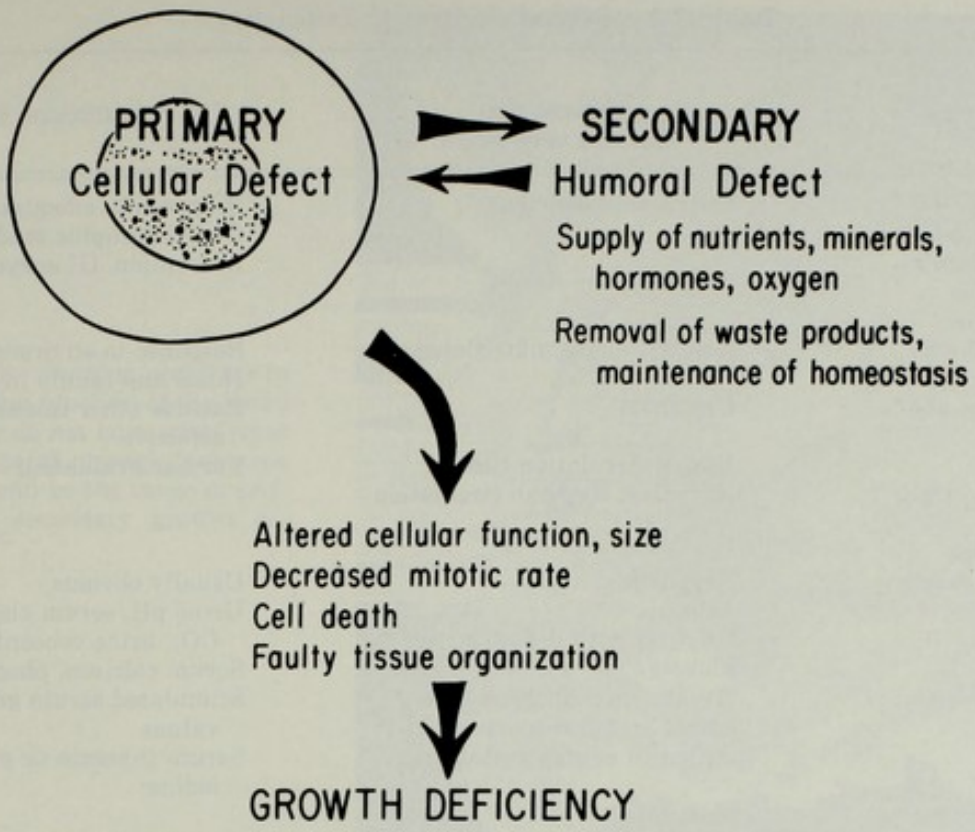


Figure 2.1. Growth deficiency may be either the consequence of a primary problem within the skeletal cells or secondary to a problem outside the skeletal cells.

patient often presents with a *pattern* of multiple malformations, the recognition of which may allow for a concise overall diagnosis.

Postnatal growth generally proceeds at a consistently slow pace. Although the anomalous skeletal development may lead to difficulty in the interpretation of "bone age," maturation usually advances at a near-normal rate, and adolescence is achieved at a usual age. As yet there is no known therapy for increasing the eventual stature for any one of the disorders within this category. The prognosis for stature can best be inferred from knowledge of the final height attainment of other patients with the same disorder.

Many of the patterns of malformation presented in this text have primary growth deficiency as one feature. These include chromosomal abnormality syndromes, osteochondrodysplasias and many other mutant gene syndromes, plus a number of syndromes of unknown etiology. For a few of them, such as the Hurler syndrome, the Hunter syndrome, and X-linked spondyloepiphyseal dysplasia, the growth deficiency does not become manifest until months or years after birth.

Secondary Skeletal Growth Deficiency. The implication for this category is that the skeletal cells are normal. The growth deficiency is *secondary* to a problem outside the skeletal system which limits its capacity for growth. The problem may reside in the delivery of nutrients, hormones, or oxygen to the skeletal cells, or in the maintenance of extracellular homeostasis. Specific types of secondary growth deficiency disorders are listed in Table 2.2. It is unusual for these types of problems to given rise to growth deficiency during fetal life* and hence the onset of growth deficiency is usually *postnatal.* As illustrated in Figure 2.2, defects in development and function of brain, pituitary, thyroid, heart, lung, liver, intestine, or kidney seldom have a serious effect on prenatal growth but can cause postnatal growth deficiency. Since the growth problem is of postnatal onset, there usually are no associated malformations, save for an anomaly which may be responsible for the growth deficiency. Furthermore, the skeletal system is normally proportioned and modelled, except in the situation of rickets.

Skeletal maturation is usually retarded to about the same extent as that of linear growth with the exception of primary hypothyroidism, in which case osseous maturation is usually relatively more retarded than is linear growth.

When the cause of the secondary growth deficiency is recognized and rectified one may witness the amazing phenomenon of catch-up

*Mild degrees of prenatal secondary growth deficiency may occur with maternal toxemia, malnutrition, or heavy cigarette smoking, and serious prenatal onset of persisting growth deficiency may occur in the offspring of women with chronic alcoholism.

Table 2.2. Secondary Growth Deficiency

PROBLEM	REASON FOR GROWTH DEFICIENCY	DIAGNOSTIC STUDIES
Nutritional a. Inadequate intake b. Partial intestinal obstruction c. Malabsorption	Nutritional deficiency	Response to adequate intake GI radiographic studies Absorption, GI enzyme studies
Deprivation syndrome	Neglect, abuse, nutritional	Response to environmental change Home and family investigation
Mental deficiency, usually severe	Unknown	Exclude other causes in mentally defective
Cardiac defect a. Large left to right shunt b. Cyanotic type	?Rapid circulation time ?Hypoxia, sluggish circulation	Cardiac evaluation
Respiratory insufficiency	?Hypoxia	Usually obvious
Renal dysfunction	Acidosis Polyuria with dehydration Rickets	Urine pH, serum electrolytes, CO_2, urine concentrating ability Serum calcium, phosphorus
Pituitary growth hormone deficiency	?Diminished lipolysis and amino acid transport to cell	Stimulated serum growth hormone values
Hypothyroidism	Deficit in energy metabolism	Serum thyroxin or protein-bound iodine
Chronic serious infectious disease (not upper-respiratory)	Unknown	
Metabolic disorders such as hypercalcemia, hypophosphatemic rickets, hypokalemia, galactosemia, glycogen storage disease, salt-losing congenital adrenal hyperplasia		

growth, an acceleration of growth and maturation toward expectancy for chronologic age. This phenomenon dramatically emphasizes the fact that there is no primary growth problem within the skeletal system. The extent of catch-up growth varies in accordance with the age of onset, duration, and nature of the growth problem—plus the adequacy of the therapy.

Prenatal Infectious Disease. Certain prenatally acquired infectious diseases such as toxoplasmosis, cytomegalic inclusion disease, and rubella may give rise to a chronic disease which can adversely affect growth, presumably by direct involvement of the skeletal system. The onset of growth deficiency is prenatal. Such babies often demonstrate other signs of prenatal infectious disease such as hepatosplenomegaly, brain dysfunction, and in the case of rubella the patient may have cataract, cardiac, and/or auditory defects. There is inadequate knowledge about the eventual growth pattern in such babies, although the growth rate may improve after one to two years of age.

CLINICAL APPROACH TO GROWTH DEFICIENCY

Emphasis should be placed on the following:

1. Family history relative to stature and maturational rate.
2. History of patient's growth, plotted on normal grids. Of particular importance is the *age of onset* of growth deficiency, and the *rate* of growth. Compare to normals for the mean parental stature when possible.
3. A complete physical evaluation should include height, weight, head circumference, and facial maturation, plus a search for major and/or minor anomalies. Check closely for evidence of malproportionment, including asymmetry. Measure span and upper-to-lower segment ratio when indicated.
4. Based on the findings, most patients can be separated into one of the following three categories:
   a. Normal for genetic background. No further studies indicated.
   b. Prenatal onset of growth deficiency. Strive to recognize a specific overall syndrome among the primary growth deficiency disorders represented in this text. Also consider prenatal infectious disease, the fetal alcohol syndrome and the fetal hydantoin syndrome.
   c. Postnatal onset of growth deficiency. Generally obtain a bone age determi-

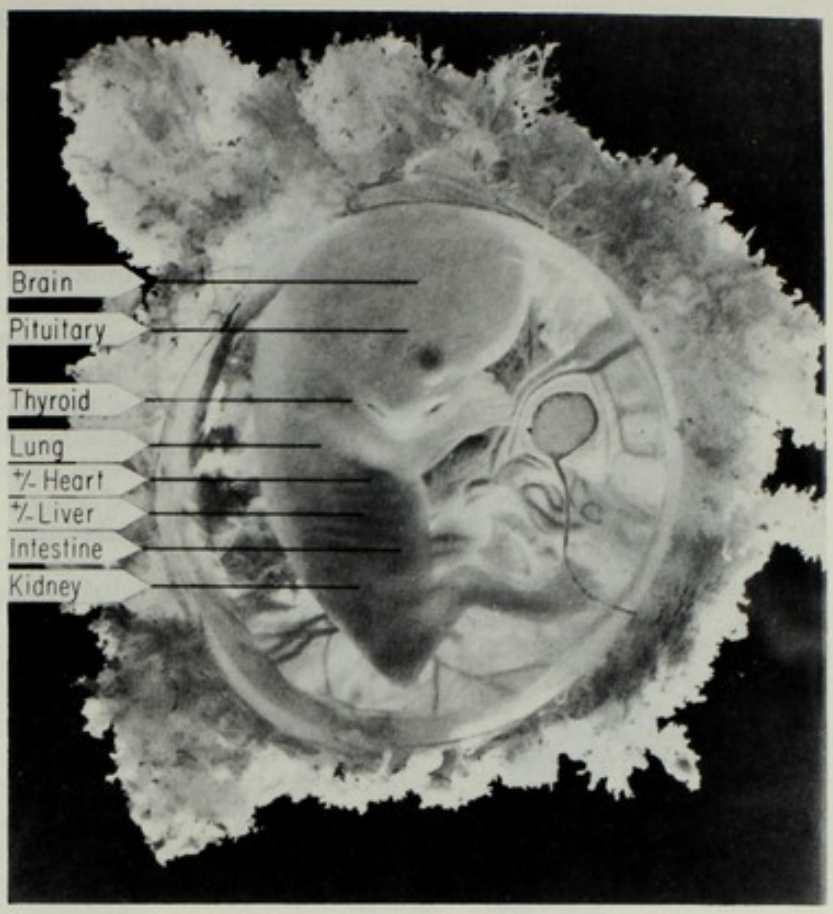


Figure 2.2. Serious problems in development and function of the listed tissues usually do not have an adverse effect on prenatal growth, whereas each problem can be the cause of serious postnatal secondary growth deficiency.

nation (roentgenographs of knee and foot prior to three months, usually just hand and wrist thereafter). Consider such secondary growth deficiency disorders as those set forth in Table 2.2 plus the few primary skeletal growth deficiency syndromes which have a postnatal onset of growth deficiency.

APPROACH TO MENTAL DEFICIENCY

Since knowledge about the development of the central nervous system (CNS) and the causes of mental deficiency is rather incomplete, the following section should be interpreted as being preliminary and tentative.

NORMAL DEVELOPMENT OF CNS[5]

At 18 days the thickened neural plate becomes a neural groove, the margins of which join to form the neural tube, which is completely closed by 28 days. Rapid growth takes place anteriorly with formation of the primitive brain vesicles: the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). By 23 days the optic outpouchings are occurring from the prosencephalon and by 33 days its lateral outpouchings, the early cerebral hemispheres, are evident. Major brain morphogenesis continues for many months; the cerebellum does not begin its major period of morphogenesis until four to five fetal months. Within the cerebral hemispheres the inner layer of neuroepithelial cells differentiate to become neuroblasts which migrate outward in successive waves to form the cortical mantle layers. By ten weeks the cerebral cortex is quite thin, with only one outer cortical layer in contrast to the relatively large size of the lateral ventricles, as shown in Figure 2.3. Cell numbers are increasing rapidly with a major addition of neurones at around four to five fetal months. New cells are being added well into postnatal life, as indicated in Figure 2.4. Although most of the neurones are present by birth, a major addition of glial cells occurs during the first six postnatal months. Most of the myelinization process, the responsibility of glial cells, occurs during the first year. The "wiring" of the axone networks, so integral to advancing and integrated function, is also occurring; however, less is known about critical periods for these interconnections between neurones. The functional consequences of this rapid brain growth and integration of neurones are reflected in the orderly progression of ad-

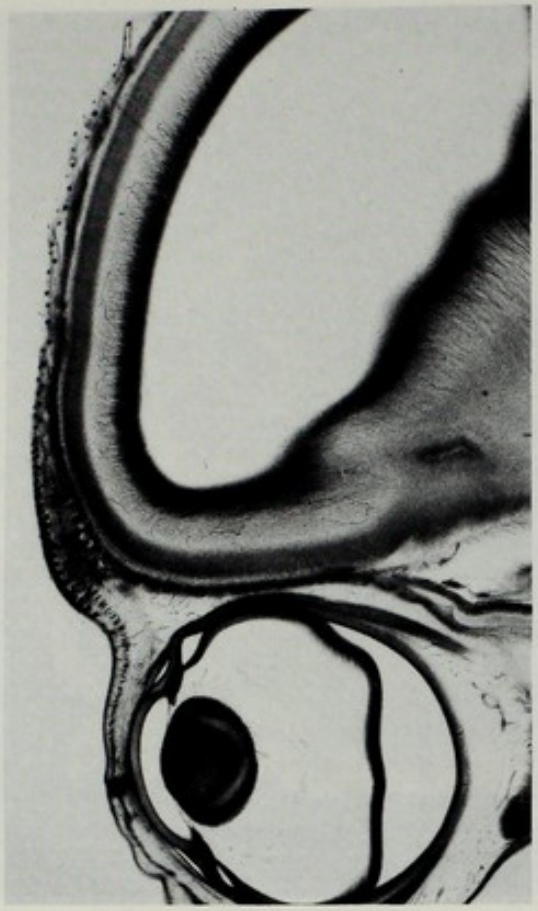


Figure 2.3. Sagittal section of fetal brain at the level of the eye at ten weeks of development. Note the single cortical zone of the cerebral cortex and the relatively large ventricular space. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)

vancing performance during this time. Brain growth is almost complete by two years, with the organ reaching about 80 per cent of its adult size by this age.

APPROACH TO PROBLEMS IN WHICH MENTAL DEFICIENCY IS A FEATURE

Clinical Subcategorization of Mental Deficiency, Relative to Diagnostic Studies

The majority of children with milder degrees of mental deficiency, having intelligence quotients (I.Q.'s) in the range of 50 to 70, come from mentally dull and/or socioeconomically deprived parentage, related to polygenic and/or environmental factors.[6] This group also contains some XXY boys, an occasional XXX girl, some malformation syndromes, and some patients with inborn errors of metabolism, milder defects of central nervous system (CNS) development, or residual CNS insults. Among the more severely mentally deficient patients, with I.Q.'s below 50, the clinician is more likely to arrive at a precise overall diagnosis. Though the following categorical breakdown of mental deficiency is especially relevant for patients with severe deficiency, it is applicable for all degrees of mental deficiency.

This general subcategorization of mental deficiency was designed to be of clinical value to aid in the rational diagnostic evaluation of a given patient with mental deficiency. It is based on findings derived from an appropriate family history, prenatal and birth history, postnatal history, and physical examination, with the latter including a cautious search for associated major and minor malformations. Having obtained such information, it is the author's contention that there is no single laboratory study which is indicated for all patients with evidence of mental deficiency. Rather, the further diagnostic evaluation should be individualized in accordance with the findings from the history and physical examination. This subcategorization is predominantly based on the apparent *age of*

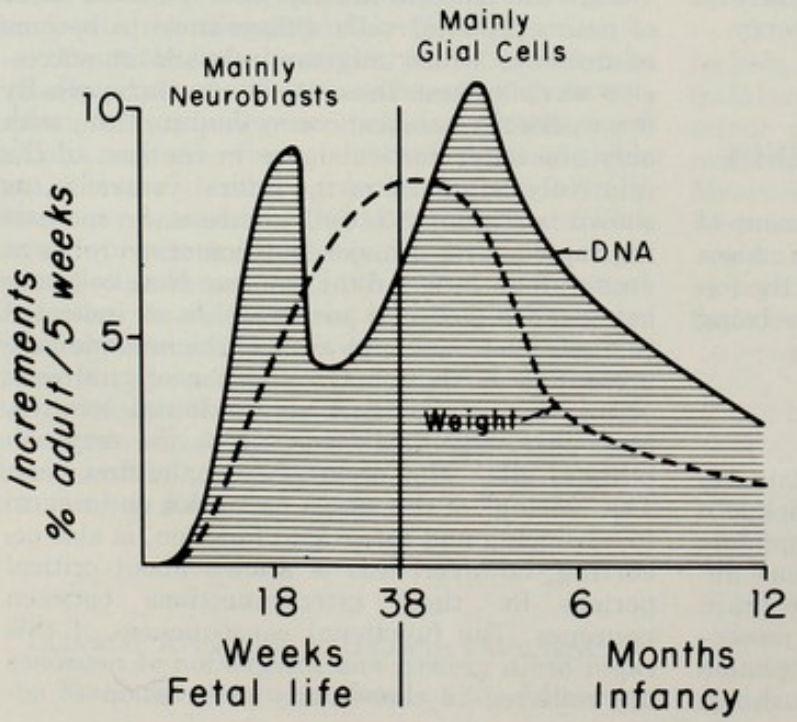


Figure 2.4. Rate of brain growth in terms of new cells (DNA) and weight during the most critical period of brain morphogenesis. (Adapted from Dobbin, J.: Am. J. Dis. Child., *120*:411, 1970.)

MENTAL DEFICIENCY

CATEGORY	SUBGROUPS	STUDIES to CONSIDER
44% PRENATAL ONSET OF PROBLEM IN MORPHOGENESIS	Single defect of brain ----- 14 %	Consider pneumoencephalography
	Multiple defect including brain	
	a. Chromosomal ---------- 12 %	Chromosome studies
	b. Unknown ---------- 6 %	Chromosome studies
	c. Known syndrome, not chromosomal ---------- 6 %	
?3% PERINATAL INSULT TO BRAIN	Trauma	
	Metabolic	
	Infectious	
?12% POSTNATAL ONSET OF PROBLEM	Environmental	
	Metabolic disorders, including known inborn errors ---------- 4 %	Indicated metabolic study
	Infectious	
	Other	
41% UNDECIDED AGE OF ONSET OF PROBLEM		Consider metabolic studies, buccal smear for X-chromatin, chromosome study
? VERY SMALL % Disorders which might present clinically in several of the above categories	Prenatal infectious disease ------	Appropriate culture and/or antibody studies
	Hypothyroidism, congenital	P. B. I. or T_4

Figure 2.5. Categorization of patients with mental deficiency, as an aid toward rational diagnostic evaluation. The percentage figures were obtained from Kaveggia, et al.[7] and represent the approximate per cent of each category and subgroup from the *total* of 1224 seriously mentally deficient patients in their study.

onset of the problem. Figure 2.5 summarizes the subgroups and the types of diagnostic laboratory studies which might merit consideration for each subgroup. These are elaborated upon in the following text.

Category I: Prenatal Problem in Morphogenesis of the Brain. This group is the largest one, making up 44 per cent of 1,224 seriously mentally deficient patients evaluated by Kaveggia, et al.,[7] and 53 per cent of a less severely mentally deficient group reported by Smith and Simons.[8] About one third of this subcategory of patients were considered to have a single primary defect in brain morphogenesis such as primary microcephaly, hydrocephalus, hydranencephaly, a defect of neural tube closure, or other types of cerebral dysmorphogenesis. The other two thirds had multiple major and/or minor malformations of non-CNS structures, and by inference the mental deficiency was also considered to be the consequence of a defect in early morphogenesis of the brain. This latter discrimination is often dependent upon a cautious total physical examination with the purpose of detecting minor as well as major anomalies. For example, Smith and Bostian[9] evaluated 50 consecutive patients with idiopathic mental deficiency and found that 42 per cent of them had three or more extra-CNS major and/or minor anomalies of prenatal onset, versus none with

three or more associated anomalies in 100 concomitantly examined control children without mental deficiency. Within Kaveggia's multiple defect subcategory 41 per cent of patients had a chromosomal abnormality, mostly the Down syndrome, 18 per cent had known syndromes of non-chromosomal etiology, and 41 per cent had unknown patterns of malformation.

Category II: Perinatal Insult to Brain. This group includes kernicterus, severe neonatal hypoglycemia, intracerebral hemorrhage, perinatal hypoxia, and meningitis and sepsis—all more common in the prematurely born infant. Caution should be exerted before assuming that problems of birth and perinatal adaptation are the *primary* cause of mental deficiency in patients who have evidence of *prenatal* onset of a problem in morphogenesis. Such patients, especially those who have a severe defect of early brain development and those with prenatal onset of growth deficiency, are more likely to have problems in neonatal adaptation.

Category III: Postnatal Onset of Problem in Brain Function. These patients generally appear normal as newborns. After a variable period of time, during which they have normal appearance and function, there is a slowing and/or deterioration in developmental progress and performance. This group includes environmental insults such as trauma, meningitis, encephalitis, hypernatremia, water intoxication, severe hypoglycemia, severe hypoxemia and lead encephalopathy, plus certain enzymatic defects of amino acid, carbohydrate, uric acid, mucopolysaccharide, and brain lipid metabolism. Though some of these latter inborn errors of metabolism may have a prenatal onset, only a few of them, such as the Leroy I-cell syndrome or generalized gangliosidosis, have gross clinical manifestations by the time of birth. Thus the *clinical* implication is usually that of a postnatal onset of the problem. Kaveggia, et al.[7] found that 4.3 per cent of the 1,224 seriously mentally deficient patients had established inborn errors of metabolism, of which one third had phenylketonuria.

Category IV: Undecided Age of Onset of the Problem in Brain Function. These are the patients who show no obvious evidence of a prenatal problem in morphogenesis, have no established history of a gross insult to the brain in the perinatal period, and who have been rather consistently slow in postnatal developmental progress, without evident cause. They may or may not have other evidence of CNS dysfunction such as spasticity, hypotonia, seizures, and/or aberrant behavior. This is the second largest group, making up 41 per cent of the series studied by Kaveggia, et al.[7]

Disorders Which May Present Clinically in Several of the Four Categories

1. *Prenatal infectious disease.* The patient with mental deficiency as a consequence of prenatally acquired infectious disease such as rubella, cytomegalic inclusion disease, or toxoplasmosis may have obvious historical and physical indications of prenatal onset of the disorder, may have had serious problems in perinatal adaptation, or may have had no obvious problems until a later age. Thus their clinical presentation may be in any one of the above categories.

2. *Congenital hypothyroidism.* Early detection of congenital hypothyroidism, with thyroid hormone replacement, is critical in preventing or at least limiting the adverse effect of hypothyroidism on early brain development.[10] Signs of prenatal onset of osseous immaturity, such as unusually large fontanels[11] and facial immaturity, are usually present at birth and perinatal problems not uncommonly include persisting indirect bilirubinemia, lethargy, and/or poor feeding. Unfortunately congenital hypothyroidism is seldom detected on the basis of these early signs and symptoms. Most commonly it is not suspected until postnatal onset of slow growth, sluggish activity, myxedema, and lag of developmental progression become evident. Patients with partial degrees of congenital hypothyroidism may not show signs of myxedema and may have a very subtle postnatal onset of slowness in growth, maturation, and developmental progress, with borderline sluggishness in activity. Thus the clinician could interpret the patient as belonging in any of the above categories, though they obviously belong in Category I (prenatal onset).

Diagnostic Studies in Patients with Mental Deficiency—Their Rational Usage:

1. Studies which may resolve the diagnosis:
   a. *Chromosomal and X-chromatin studies:* Indications for chromosome studies are largely limited to appropriate patients in Category I who have multiple malformations. Buccal smear for X-chromatin is merited for patients in Category IV (undecided) when the clinical findings do not *exclude* the possibility of XXY or XXX. Should the findings be suggestive of XYY a chromosome study or Y-chromatin study is merited.
   b. *Studies for inborn errors of metabolism:* Patients with mental deficiency due to an inborn error of metabolic function, most commonly the consequence of a recessively inherited enzyme defect, often have one or more additional clues besides mental deficiency alone. Some of these are set forth in Table 2.3. These patients usually fit into Category III. They appear normal at birth and then at variable postnatal ages develop diffuse non-lateralizing evidence of central nervous system deficit or deterioration

Table 2.3. Examples of Features in Addition to Mental Deficiency Which Often Occur Postnatally in Certain Inborn Errors of Metabolism.[12]

DISORDER	FEATURES
Phenylketonuria, classical; autosomal recessive	Light pigmentation; eczema (33%); poor coordination, seizures (25%), autistic behavior
Sanfilippo syndrome (MPS III); autosomal recessive	Developmental lag after 1 year with deterioration toward restless behavior, clumsiness by age 6–7 yrs; development of coarse facies and hair by 2–3 yrs; gum hypertrophy, mild limitation in finger extension
Hurler syndrome (MPS I); autosomal recessive	Developmental lag after 6–10 mos, with deterioration and growth deficiency, coarse facies, stiff joints, gibbus, hepatosplenomegaly, cloudy corneas, rhinitis
Hunter syndrome (MPS II), severe type; X-linked recessive	Developmental lag after 6–12 mos. with growth deficiency, coarse facies, stiff joints, hepatosplenomegaly; no gibbus or cloudy corneas
Galactosemia, severe type; autosomal recessive	Development in early infancy (on cow's milk feeds) of lethargy, hypotonia, hepatomegaly, icterus, hypoglycemia, cataract, with failure to thrive
Lesch-Nyhan syndrome; X-linked recessive	Development after 6–8 mos. of spasticity, choreoathetosis, self-mutilation, autistic behavior, growth deficiency; tophi in late childhood
Homocystinuria; autosomal recessive	Mild arachnodactyly, pectus, genu valgus, pes cavus, mild limitation of finger extension; downward lens dislocation, usually by age 10 yrs; wide facial pores, malar flush; thrombotic phenomena, contributing to CNS problems
Argininosuccinicaciduria; autosomal recessive	Onset in first 1–2 yrs. of growth deficiency, mild hepatomegaly, skin lesions, dry brittle hair with trichorrhexis nodosa, seizures

of function. A history of intermittent lapses of consciousness, inanition, unexplained hypoglycemia, or recurrent acidosis should each be potential clues toward an inborn error of metabolism. For example, acidosis may be a feature of lactic acidemia, and intermittent loss of consciousness may occur in the severe form of maple syrup urine disease or in hyperammonemia.

Phenylpyruvic oligophrenia may be difficult to suspect from the clinical findings. When it cannot be excluded as a possibility by the overall features, a urine ferric chloride test or a serum phenylalanine determination should be done.

c. *Studies for prenatal infectious disease:* Patients with mental deficiency as the result of congenital rubella, cytomegalic inclusion, or toxoplasmosis disease usually also have one or more of the following features: microcephaly, chorioretinitis, prenatal onset growth deficiency, hepatosplenomegaly, neonatal petechiae, and/or jaundice or deafness. Patients with congenital rubella may also have cataract, cardiac defect, and other anomalies. Those mentally deficient patients who have one or more of these additional findings, and whose total findings do not *exclude* the possibility of the disorder being due to prenatal infectious disease, should be considered for one or more of the following studies: direct culture of the infectious agent (in early infancy), specific fluorescent IgM antibody determination, and complement-fixation antibody determination.

d. *Thyroid studies:* A P.B.I or serum thyroxine determination is merited for the mentally deficient patient who has evidence of osseous immaturity, slow postnatal growth, sluggish physical activity, and myxedematous fullness in the tissues. Thyroid studies are *not* indicated in the patient with mental deficiency and short stature who does not show any other clinical indication of being hypothyroid.

2. Ancillary studies which may assist in the diagnosis:

a. *Pneumoencephalography* may occasionally be indicated in a Category I patient with a primary defect in brain morphogenesis in an effort to delineate the nature and extent of the brain malformation more fully. This may be of particular relevance for hydrocephalus. For other defects the study may provide a better perspective toward prognosis as well as genetic counselling.

b. *Skull roentgenograms* merit consideration in a patient with clinical signs of

craniosynostosis, evidence of increased intracranial pressure, cutaneous signs of tuberous sclerosis or Sturge-Weber anomalad, or evidence of prenatal infectious disease, especially toxoplasmosis. Otherwise there is seldom any clinically relevant information to be derived from this study.

c. *Long bone roentgenograms* may be indicated by clinical findings such as skeletal abnormalities. Bone age determination may be indicated in patients with decelerating growth, especially those in whom the overall findings are compatible with hypothyroidism, and in patients with excessive rate of growth, but is of little practical value in patients with prenatal onset of growth deficiency.
d. *Electroencephalograms* may be warranted in patients with a history of seizures or suspected seizure-equivalent.
e. *Fasting blood glucose* merits consideration in patients with a history suggestive of hypoglycemic signs and symptoms but is not necessarily indicated for all patients with seizures.
f. Other serum chemistries, blood studies, and urinalyses should be performed only as prompted by findings other than mental deficiency in the history or examination.

APPROACH TO ARTHROGRYPOSIS (Prenatal Onset of Joint Contractures)

Normal Development of Joints

Joint development begins secondarily within the early mesenchymal condensations of the precartilaginous bone at about five and one-half weeks. By seven weeks many joint spaces exist and by eight weeks there is movement of the limbs. Figure 2.6 shows the early development. Motion is essential for the normal development of the joints and their contiguous structures.

Problems Which Can Cause Congenital Joint Contractures (see Figure 2.7)

1. *Neurologic abnormality* has been the most common cause of arthrogryposis, in the experience of the author. The neurologic disorders which may be responsible for the secondary arthrogryposis include: meningomyelocele, anterior motor horn cell deficiency, prenatal spasticity, and certain gross brain defects such as anencephaly, hydranencephaly, and holoprosencephaly. An example is shown in Figure 2.8.

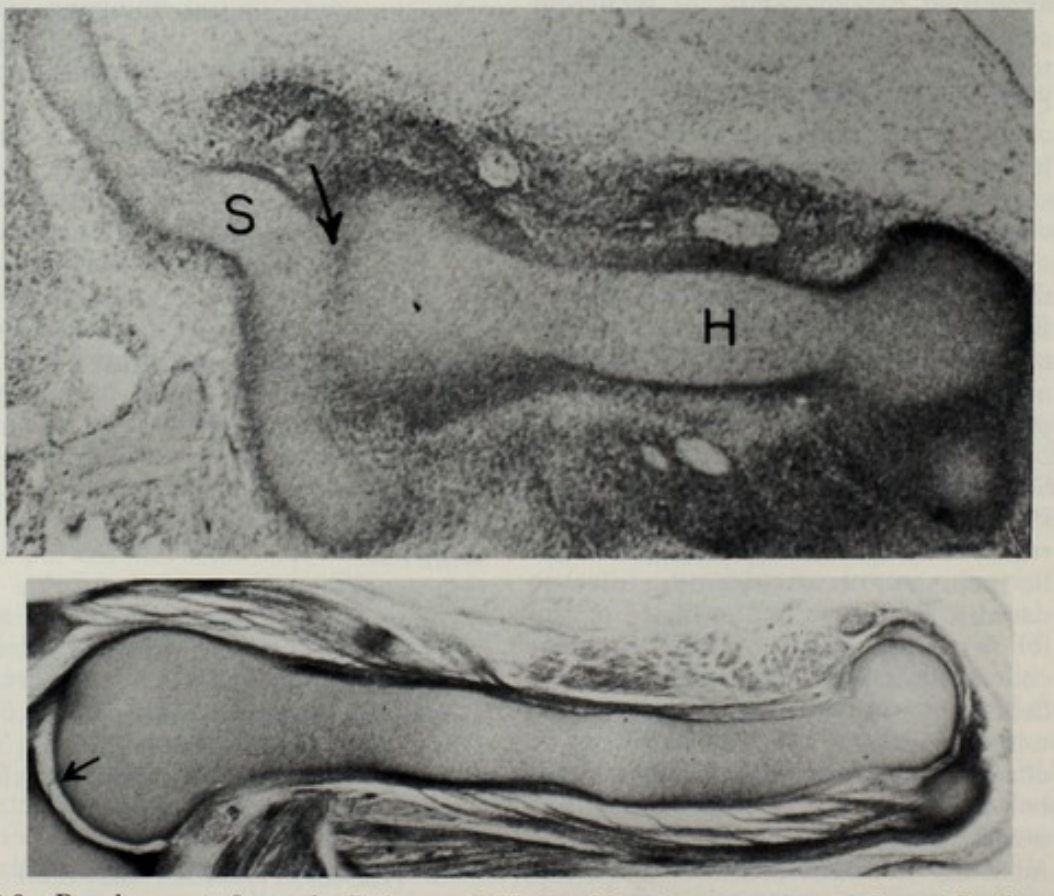


Figure 2.6. Development of scapulo (S)–humoral (H) shoulder joint (*arrow*) at 38 days of development (*above*) and at about 47 days (*below*). Note that joint morphogenesis occurs secondarily. By the time the joint is formed, functional muscle has differentiated.

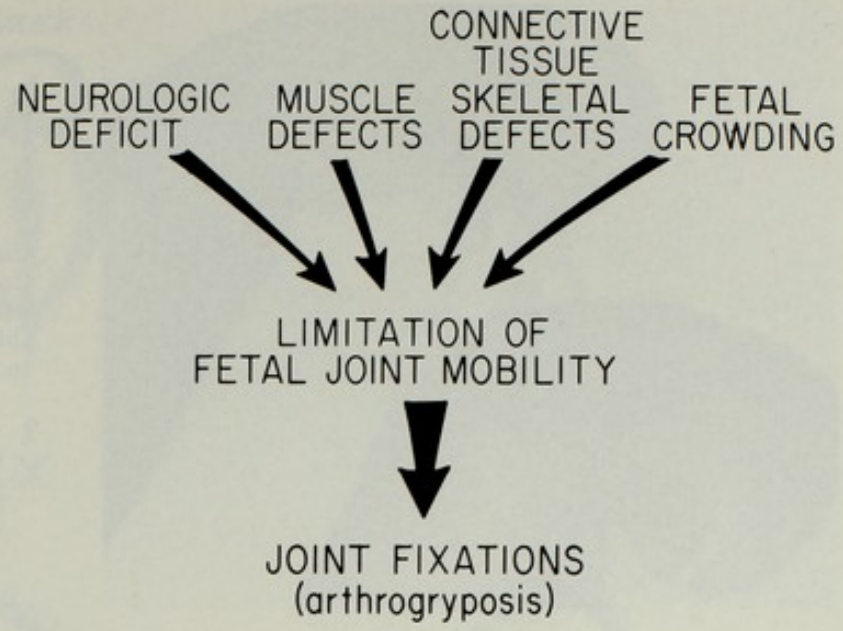


Figure 2.7. The types of problems which can lead to prenatal joint contractures.

2. *Muscle problems* such as muscle agenesis, rare fetal myopathies, and occasionally in myotonic dystrophy (see p. 114).

3. *Joint and contiguous tissue problems* such as synostosis, lack of joint development, aberrant fixation of joints as in diastrophic dwarfism, aberrant laxity of joints with dislocations as in the Larsen syndrome, and aberrant soft tissue fixations such as in the popliteal web syndrome.

4. *Fetal crowding and constraint* such as with multiple births or with oligohydramnios in disorders such as renal agenesis or early persisting leakage of amniotic fluid.

METHODS OF EVALUATION

1. *History:* The history relative to arthrogryposis should include information on the onset and character of fetal movements (often diminished), mode of delivery (often breech), and amniotic fluid (oligohydramnios may give rise to fetal crowding).

2. *Total pattern of anomalies:* Non-joint-related anomalies may indicate that the arthrogryposis is a part of a multiple defect syndrome such as the trisomy 18 syndrome.

3. *Joint and skeletal evaluation:* Physical and radiologic assessment of joints and skeletal system. Determine whether the joint fixation is due to an anatomical anomaly such as lack of development of a joint, to synostosis, to soft tissue webs, or to a deficit in functional movement with no primary structural cause. Always check for scoliosis and for hip dislocation.

4. *Evaluation of hand and foot creases:* The palmar and finger creases and the sole creases represent the planes of early flexional function and are evident by 11 to 12 weeks of fetal age. Absent or abnormal creases are secondary to aberrant form or function in the early hand or foot development. They also provide a historical

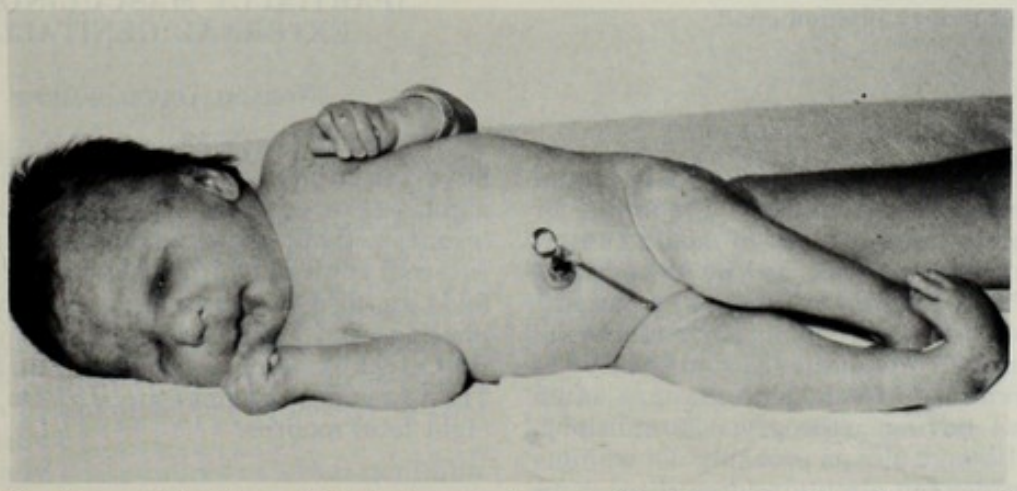


Figure 2.8. Aberrant fixations of all joints, most dramatically in hands and feet, interpreted as being the consequence of a gross neurologic deficit with prenatal hypertonicity. The neurologic dysfunction was considered secondary to a severe early defect in brain development, including early optic cup and eye development (microphthalmia).

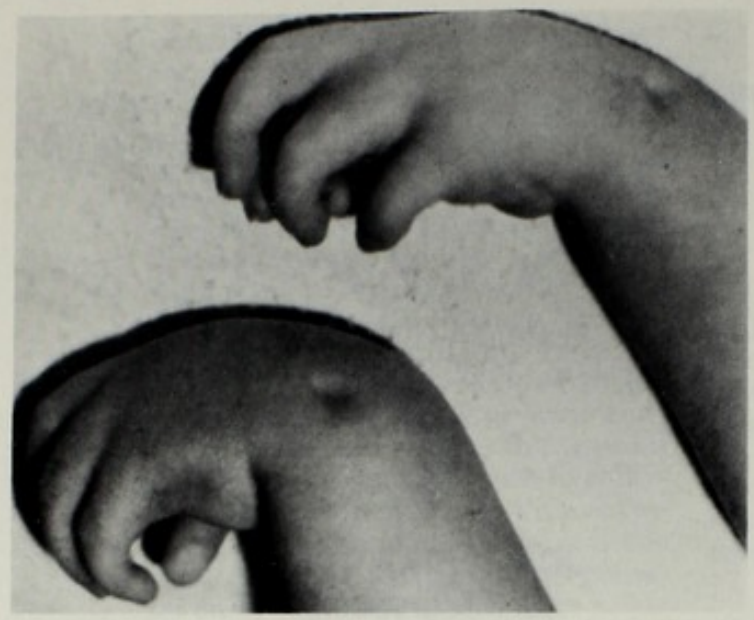


Figure 2.9. Dimples on the dorsum of the wrists, indicating that the aberrant positioning of the hands had been present from early in fetal life. The joint contractures in this infant were considered to be secondary to neurologic deficiency.

record of the flexional planes of function which have existed, and thus facilitate decisions relative to rehabilitation of existing function.

5. *Search for dimples:* Where there has been close fetal contact between bone and overlying skin there may be failure in the development of subcutaneous tissue and adipose at that locale and thereby a dimple. The finding of aberrant dimples implies an early fetal onset of the problem, resulting in aberrant cutaneous-osseous approximation as shown in Figure 2.9.

6. *Cautious neurologic and muscle assessment:* Attempts to determine whether there is a primary neurologic or muscle problem can be most difficult since deficit in either one can lead to aberrant function of the other. Electromyographic (EMG) studies occasionally may be of value. In the great majority of patients with arthrogryposis in whom this study is abnormal, the evidence points toward neuropathy, and rarely to a myopathy. Muscle biopsy may only occasionally be of value since it is difficult to determine whether muscle hypoplasia and/or fibrosis is a primary or secondary phenomenon.

Comment and Management

When a particular diagnosis can be delineated, the management should be specific for that disorder, including a lack of medical intervention for such disorders as the trisomy 18 syndrome. There remains a number of patients with multiple congenital joint contractures for whom no specific diagnosis can presently be clearly determined. Such patients are often designated as having arthrogryposis multiplex congenita, although this is probably not a single etiologic disorder but simply a loose clinical categorization. Such patients most commonly have fusiform partially fixed joints with muscle wasting. The most common joints affected are in the feet (equinovarus). Multiple other joints may be affected, the hips are often dislocated, and scoliosis is not infrequent. Fisher, et al.[13] studied 26 such patients and noted the following generalities:

1. Of 20 patients having electromyography, 18 indicated neuropathy, one myopathy, and one was normal.
2. Despite serious deformity, the majority of patients became ambulatory.
3. No single mode of management was effective in all patients.

In general only limited upper limb improvement was achieved by nonsurgical means, attempts at reduction of dislocated hips were seldom successful, and a variety of aggressive approaches toward knee and foot contractures were often necessary.

APPROACH TO AMBIGUOUS (PARTIALLY MASCULINIZED) EXTERNAL GENITALIA

Normal Development

Genes on the Y chromosome confer testicular differentiation of the gonad which at about eight weeks gestation begins producing testosterone, actively causing masculinization of the external genitalia with fusion of the labioscrotal folds to form a scrotum, enlargement of the phallus, and fusion of the labia minora folds into a penile urethra, as shown in Figure 2.10. The testes descend into the scrotum by seven to eight fetal months.

Causes of Aberrant Development[14, 15]

Partial masculinization of the external genitalia, including incomplete descent of the testi-

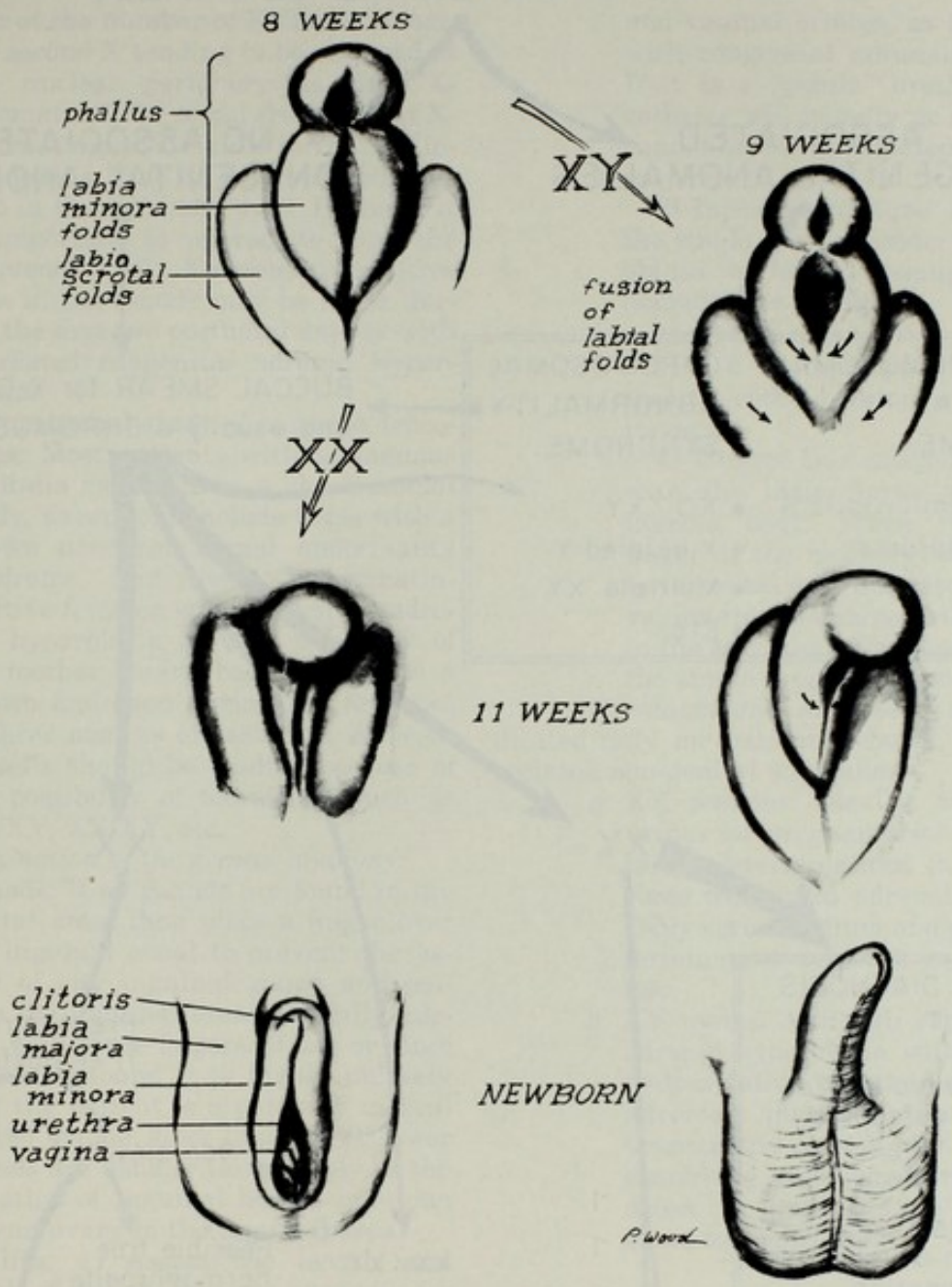


Figure 2.10. Normal morphogenesis of external genitalia. The normal male development is induced by testosterone derived from the fetal testicle. (Illustrations adapted from photos supplied by J. Jirasek, Prague.)

cles, can be secondary to any one of the following problems:

1. Diminished fetal androgen production because of a defect in development and/or function of the testicles.
2. Diminished to absent cellular response to androgen (testosterone) in the male.
3. Primary defect in development of external genitalia in the male, not secondary to hormonal aberration.
4. Partially masculinized external genitalia due to exposure of the XX female to androgen in utero. The androgen may derive either from the fetus (e.g., congenital adrenal hyperplasia) or from the mother during early gestation.

METHODS OF EVALUATION (see Figure 2.11)

1. *Complete examination for associated non-genital anomalies:* If significant non-genital anomalies are present, then it is highly unlikely that the patient has congenital adrenal hyperplasia or any other known defect in steroidogenesis. An attempt should then be made to identify the total pattern of malformation from among known syndromes such as the Smith-Lemli-Opitz syndrome, etc., in which genital anomaly is one feature of a multiple defect disorder.
2. *Determination of genetic sex:*
   a. Buccal smear for X-chromatin: This procedure will assist in the determina-

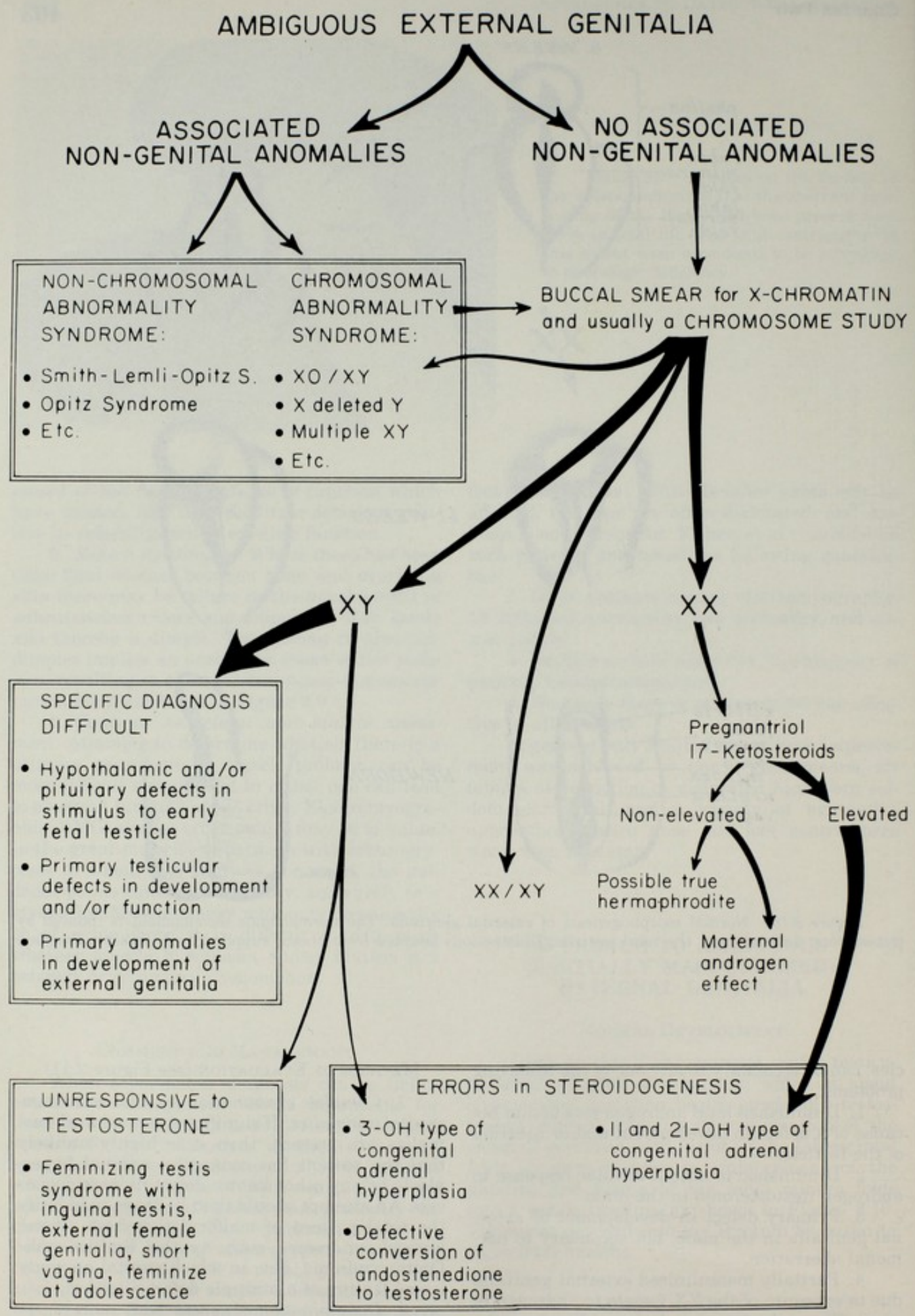


Figure 2.11. Approach toward arriving at a specific overall diagnosis in the patient who has ambiguous external genitalia.

tion of the number of X chromosomes, the second X tending to be clumped at the nuclear periphery as the "X-chromatin." The usual frequency of X-chromatin-positive cells in the XX individual is 19 to 35 per cent and near zero in the XY individual. However it is important to appreciate that the frequency of X-chromatin-positive cells in the female may be lower during the first two postnatal days or with untreated congenital adrenal hyperplasia.

b. Chromosomal study of cultured leucocytes: Most patients with ambiguous genitalia should have a chromosomal study. Exceptions include those with a known nonchromosomal abnormality syndrome, and those X-chromatin-positive females with congenital adrenal hyperplasia or with a history of the mother having been exposed to a known androgen during the first two to three months of gestation. At least 20 cells should be studied because of the possibility of mosaicism such as XO/XY, XX/XY, etc.

3. *Determination of the genital anatomy:*

a. Gonads: If no gonads are found in the scrotal area, then place a finger over the inguinal canal to prevent the ascent of any inguinal gonad and palpate the inguinal areas carefully, ideally with three fingers. If one or more gonads is found it is highly unlikely that the patient is a partially masculinized female, since inguinal or lower gonads are usually testes. Only in the situation of inguinal hernia may one find an ovary in the inguinal area.

b. Phallus: 1) Assess the length and width of the phallus (see appendix for standards). If it is a relatively thin phallus it is unlikely to be female with congenital adrenal hyperplasia, since she would be under "active" androgen stimulation with increased caliber to the phallus.

2) If there is a single opening at the base of the phallus and also a small "pit" on the glans, the former represents the urethral opening and the latter is of no significance.

c. Urogenital sinus or urethra; vagina; uterus: 1) When there is but a single opening at the base of the phallus, insert a relatively stiff catheter or sterile probe into it. Direct the catheter tip downward in the direction of the anal opening. If it goes in that direction easily and can be palpated beneath the perineal skin then there is probably a urogenital sinus with both urethral and vaginal orifices, as in the female with congenital adrenal hyperplasia. If it is a "penile" urethra then the catheter will usually go cephalad and cannot be easily palpated in the perineal area.

2) Inject radiopaque material into the single opening under pressure and obtain a lateral roentgenogram to demonstrate whether there is a vaginal pouch or not.

3) If a vaginal opening is evident, insert a catheter into it and determine its depth.

4) Uterus: Do a cautious rectal exam with the little finger, feeling for a uterine body. When removing the finger in the newborn, stroke the anterior rectal area outward. If there is a vagina this maneuver will often result in the extrusion of vaginal mucus from the single urogenital opening.

4. *Hormonal and metabolic studies* are indicated only for patients who do not have associated non-genital anomalies:

a. XX females: Ideally, three 24-hour urines for pregnanetriol and 17-ketosteroid determinations in order to exclude congenital adrenal hyperplasia. Daily serum sodium and potassium determinations to detect evidence of salt loss.

b. XY males: Although rare, congenital adrenal hyperplasia with defective 3-hydroxylation or other defects which adversely affect the steroidogenesis of testosterone as well as hydrocortisone should be considered, as well as a defect in conversion of androstenedione to testosterone.

MANAGEMENT

The initial evaluation of the newborn baby with ambiguity in the development of the external genitalia, including those with fully developed penis but no testes palpable, constitutes an emergency situation relative to sex of rearing. The XX individuals with congenital adrenal hyperplasia (the most common single cause of ambiguous genitalia) and those females partially masculinized in utero by maternal androgen should be raised as females with appropriate cosmetic surgery. Exploratory surgery for gonadal and internal genital anatomy should usually precede a sex of rearing decision in the rare situations of the XX/XY individual or the XX patient who has neither congenital adrenal hyperplasia or a history compatible with maternally derived in utero androgen effect. For the great majority of the remaining patients, the sex of rearing is dependent upon the adequacy of the phallus to be a cosmetically and functionally

adequate penis. When this is not possible, the sex of rearing should be female with appropriate cosmetic surgery. In some of the borderline cases in which the male sex of rearing would seem preferable, the author has utilized a short course of Depo-Testosterone therapy in low dosage, 25 mg every three weeks for three months, in order to enlarge the penis during early infancy.[16] This has resulted in a one and one-half- to two-fold enlargement of the penis, thus allowing for better parental acceptance (especially paternal!) and early cosmetic surgery for hypospadias. The rationale for this therapy is based on the supposition that most of these cases represent inadequate androgen effect from the fetal testicle in bringing about full size development of the penis; hence, exogenous testosterone is given for a short period of time in order to enlarge the incompletely developed penis. Beyond the phallic enlargement, no other signs of virilization have been noted during this type of short-term, low-dosage course of testosterone. Transient mild to moderate acceleration of growth and skeletal maturation have occurred, tending to fall back to a normal rate after testosterone. Hence, no appreciable effect of this therapy is anticipated in terms of ultimate growth.

The author prefers to have testosterone enlargement of the phallus (when indicated) and/or cosmetic surgery to the external genitalia accomplished before 18 months to two years of age, with the exception of creating a vaginal pouch. The purpose of this approach is to have the external genital anatomy as appropriate as possible for sex of rearing before the age when the individual will be fully cognizant of sex and gender orientation.

Because of the tumor and malignant risk, removal of intraabdominal testicular tissue is generally indicated unless it appears near-normal and can be brought into the scrotum. This need not necessarily be accomplished during childhood, with the probable exception of the XO/XY mosaic. The dysmorphic testicle, such as may be found in XO/XY patients, has a significant risk of tumor development, even prior to adolescence.

REFERENCES

Growth Deficiency

1. Faulkner, F., ed.: Human Development. Philadelphia, W. B. Saunders Co., 1966.
2. Gardner, L. I., ed.: Endocrine and Genetic Diseases of Childhood. 2nd ed. Philadelphia, W. B. Saunders Co., 1975.
3. Garn, S. M., and Rohmann, C. G.: Interaction of nutrition and genetics in the timing of growth and development. Pediatr. Clin. North Am., *13*:353, 1966.
4. Tanner, J. H., Goldstein, H., and Whitehouse, R. H.: Standards for children's height at ages two to nine years allowing for height of parents. Arch. Dis. Child., *45*:755, 1970.

Mental Deficiency

5. O'Rahilly, R., and Gardner, E.: The timing and sequence of events in the development of the human nervous system during the embryonic period proper. Z. Anat. Entwicklungsgesch., *34*:1, 1971.
6. Drillien, C. M., Jameson, S., and Wilkinson, E. M.: Studies in mental handicap, Part I: Prevalence and distribution by clinical type and severity of defect. Arch. Dis. Child., *41*:528, 1966.
7. Kaveggia, E. G., Durkin, M. V., Pendleton, E., and Opitz, J. M.: Diagnostic genetic studies on 1,224 patients with severe mental retardation. Proceedings of the Third Congress of the International Association for Scientific Study of Mental Deficiency. Held at The Hague, Holland, September 4–12, 1973.
8. Smith, D. W., and Simons, F. E. R.: Rational diagnostic evaluation of the child with mental deficiency. Am. J. Dis. Child., *129*:1285, 1975.
9. Smith, D. W., and Bostian, K. D.: Congenital anomalies associated with idiopathic mental retardation. J. Pediatr., *65*:189, 1964.
10. Smith, D. W., Blizzard, R. M., and Wilkins, L.: The mental prognosis in hypothyroidism in infancy and childhood: A review of 128 cases. Pediatrics, *19*:1011, 1957.
11. Smith, D. W., and Popich, G.: Large fontanels in congenital hypothyroidism: A potential clue toward earlier recognition. J. Pediatr., *80*:753, 1972.
12. Holmes, L. B., et al.: Mental Retardation. An Atlas of Diseases with Associated Physical Abnormalities. New York, The Macmillan Co., 1972.

Arthrogryposis

13. Fisher, R. L., Johnstone, W. T., Fisher, W. H., and Goldkamp, O. G.: Arthrogryposis multiplex congenita, a clinical investigation. J. Pediatr., *76*:255, 1970.

Amgibuous External Genitalia

14. Williams, R. H., ed.: Textbook of Endocrinology, 4th ed. Philadelphia, W. B. Saunders Co., 1968.
15. Summitt, R. L.: Differential diagnosis of genital ambiguity in the newborn. Clin. Obstet. Gynecol., *15*:112, 1972.
16. Guthrie, R. D., Smith, D. W., and Graham, C. B.: Testosterone treatment for the micropenis during early childhood. J. Pediatr., *83*:247, 1973.

Chapter Three

MORPHOGENESIS AND DYSMORPHOGENESIS

Knowledge of normal morphogenesis may assist in the interpretation of malformations, and malformations may assist in the understanding of normal morphogenesis. Each anomaly must have a logical mode of development and cause. When interpreting a malformation the clinician is looking back to an early stage in development with which often he has had little acquaintance. This chapter sets forth some of the phenomena of morphogenesis and the normal stages in early human development, followed by the types of abnormal morphogenesis and the relative timing of particular malformations.

NORMAL MORPHOGENESIS

Phenomena of Morphogenesis

The genetic information that guides the morphogenesis and function of an individual is all contained within the zygote. After the first few cell divisions, differentiation begins to take place, presumably through activation or inactivation of particular genes, allowing cells to assume diverse roles. The entire process is programmed in a timely and sequential order with little allowance for error, especially in early morphogenesis.

Although little is known about the fundamental processes that control morphogenesis, it is worthwhile to mention some of the normal phenomena which occur and examples of each.

Cell Migration

The proper migration of cells to a predestined location is critical in the development of many structures. For example, the germ cells move from the yolk sac endoderm to the mesonephric ridge where they interact with other cells to form the gonad.

Control over Mitotic Rate

The size of particular structures, as well as their form, is to a large extent the consequence of control over the rates of cell division.

Interaction Between Adjacent Tissues

The optic cup induces the morphogenesis of the lens from the overlying ectoderm, the ureteral bud induces the development of the kidney from the adjacent metanephric tissue, the notochord is essential for normal development of the overlying neural tissue, and the prechordal mesoderm is essential for the normal morphogenesis of the overlying forebrain. These are but a few examples of the many interactions that are essential features in morphogenesis.

Adhesive Association of Like Cells

In the development of a structure such as a long bone the early cells tend to aggregate closely in condensations, a membrane comes to surround them, and only later do they resemble cartilage cells. The association of like cells is dramatically demonstrated by admixing trypsinized liver and kidney cells in vitro and observing them to reaggregate with their own kind.

Hormonal Influence over Morphogenesis

Androgen effect is one example of a hormonal influence over morphogenesis—in this case, that of the external genitalia. Normally the individual with a Y chromosome has testos-

terone from the fetal testicle which induces enlargement of the phallus, closure of the labia minoral folds to form a penile urethra, and fusion of the labioscrotal folds to form a scrotum. Prior to eight weeks the genitalia appear female in type and will remain so unless androgenic hormone is present.

NORMAL STAGES IN MORPHOGENESIS

The general stages in normal morphogenesis as set forth here are illustrated in Figures 3.1 to 3.13. The first week is a period of cell division without much enlargement, the conceptus being dependent on the cytoplasm of the ova for most of its metabolic needs. By seven to eight days the zona pellucida is gone and the outlying trophoblast cells invade the endometrium and form the early placenta which must function both to nourish the parasitic embryo and to maintain the pregnancy via its endocrine function. During this time a relatively small inner cell mass has become a bilaminar disc of ectoderm and endoderm, each with its own fluid-filled cavity, the amniotic sac and yolk sac respectively. By the end of the second week a small mound, Hensen's node, has developed in the ectoderm, and behind it a primitive streak forms. The embryo now has an axis to which further morphogenesis will relate. Cells migrate forward from Hensen's node between the ectoderm and endoderm to form an elastic cord, the notochord, which temporarily provides axial support for the embryo as well as influencing the adjacent morphogenesis. Ectodermal cells migrate through Hensen's node and the primitive streak to specific areas between the ectoderm and endoderm, becoming the mesoderm. One of the early mesodermal derivatives is a circulatory system; during the third week the heart begins to develop, vascular channels form in situ, and blood cells are produced in the yolk sac. By the end of the third week the heart is pumping, a neural groove has formed anterior to Hensen's node, the para-axial mesoderm has begun to be segmented into somites, the anterior and posterior regions of the embryo have begun to curl under, and the foregut and hindgut pouches become distinct. The stage is now set for the period of major organogenesis which is best considered in relation to individual structures.

Early morphogenesis is set forth in the accompanying figures. As noted in the illustrations found on the inside front cover and inside back cover of this book, each stage of development represents a synchronous syndrome of characteristics.

Text continued on page 414.

GENERAL MORPHOGENESIS

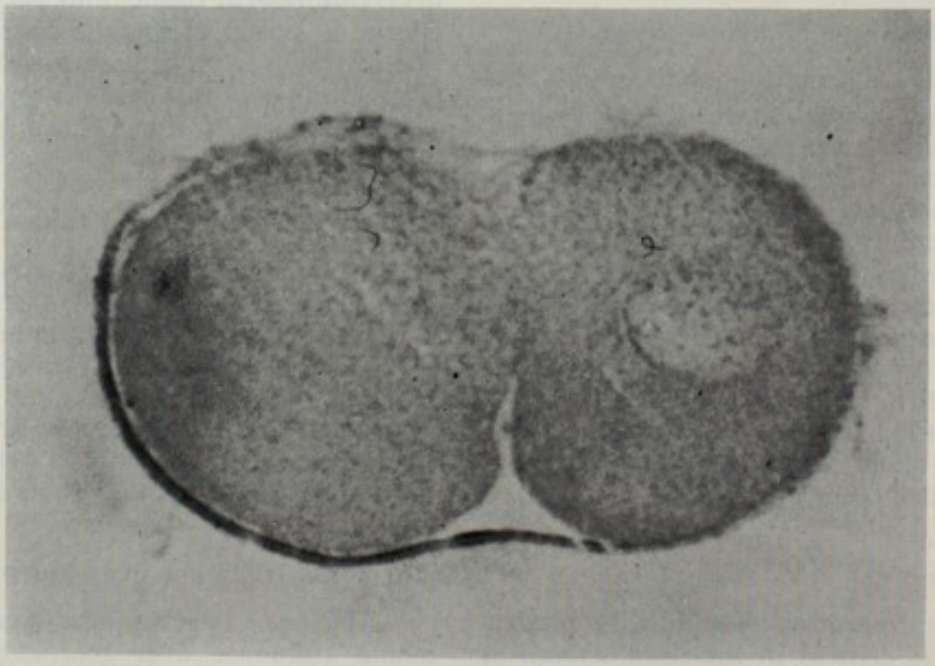


Figure 3.1. Two cell stage, within zona pellucida. (From the Department of Embryology, Carnegie Institute of Washington, D.C., Baltimore.)

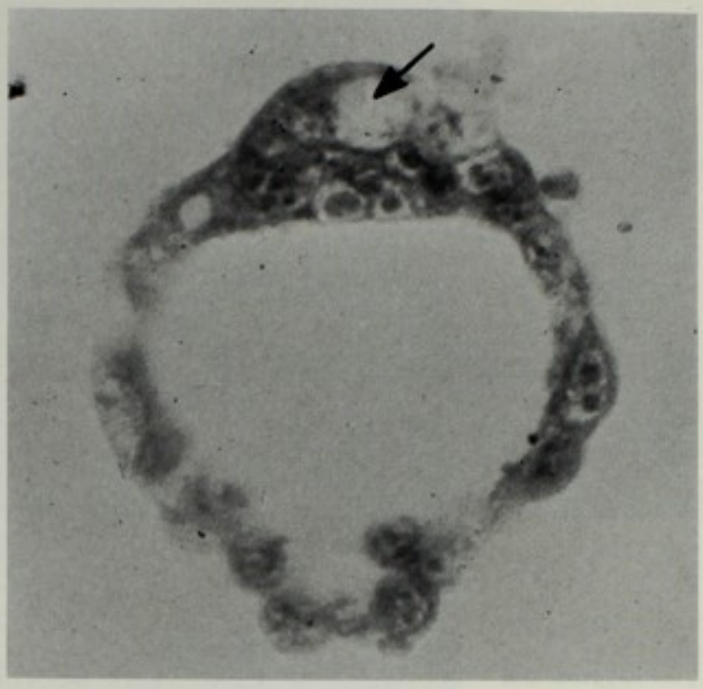


Figure 3.2. **Four to five day** blastula stage. The embryonic cell mass (*top*) shows the first indication toward an amniotic space (*arrow*). (From the Department of Embryology, Carnegie Institute of Washington, D.C., Baltimore.)

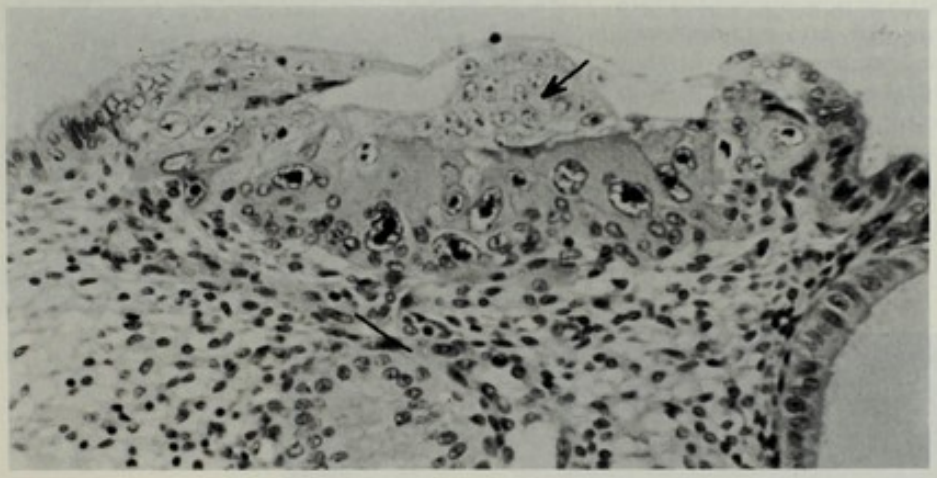


Figure 3.3. **Seven days.** The major part of the conceptus, the cytotrophoblast, has invaded the endometrium, and the embryo (*arrow*) is differentiating into two diverse cell layers, the ectoderm and endoderm. (From the Department of Embryology, Carnegie Institute of Washington, D.C., Baltimore.)

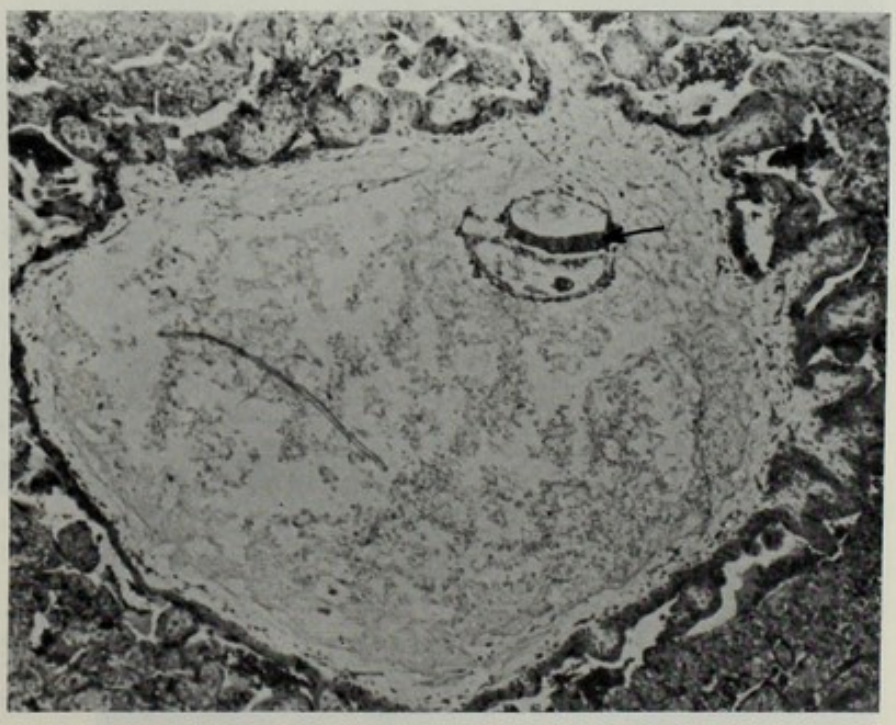


Figure 3.4. **Fourteen to sixteen days.** The thicker ectoderm (*arrow*) has its continuous amniotic sac, whereas the underlying endoderm has its yolk sac. Major changes will now begin to take place.

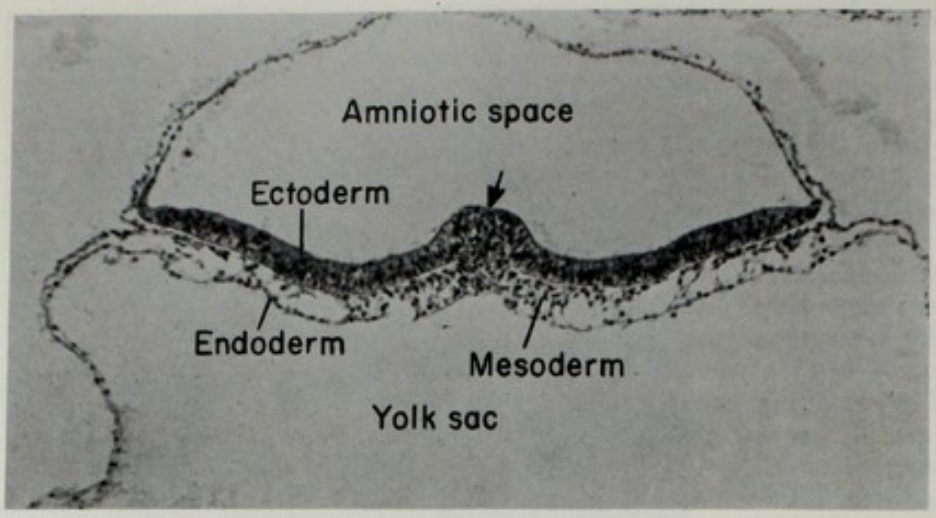


Figure 3.5. **Seventeen to eighteen days.** Mesioblast cells migrate from the ectoderm through Hensen's node (the hillock marked by the arrow) and the primitive streak to specific locations between the ectoderm and endoderm, there constituting the highly versatile mesoderm. Anterior to Hensen's node the notochord develops, providing axial support and influencing subsequent development such as that of the overlying neural plate.

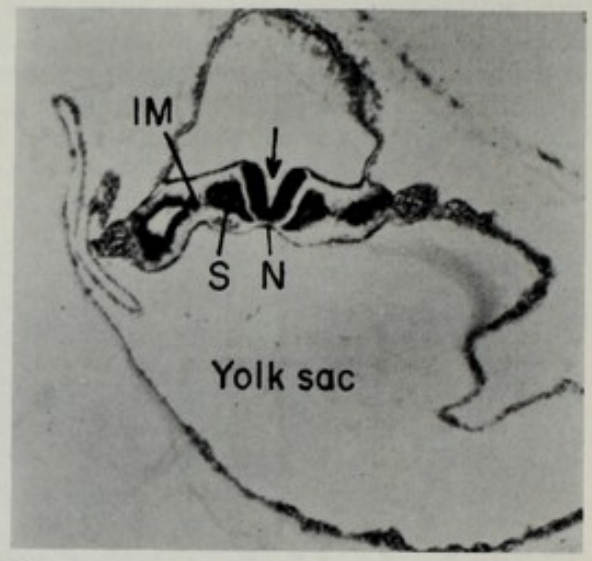


Figure 3.6. **Twenty-one to twenty-three days.** The midaxial ectoderm has thickened and formed the neural groove (*arrow*), partially influenced by the underlying notochord (N). Lateral to it the mesoblast has now segmented into somites (S), intermediary mesoderm (IM), and somatopleura and splanchnopleura as intervening stages toward further differentiation. Vascular channels are developing in situ from mesoderm, blood cells are being produced in the yolk sac wall, and the early heart is beating. Henceforth development is extremely rapid with major changes each day.

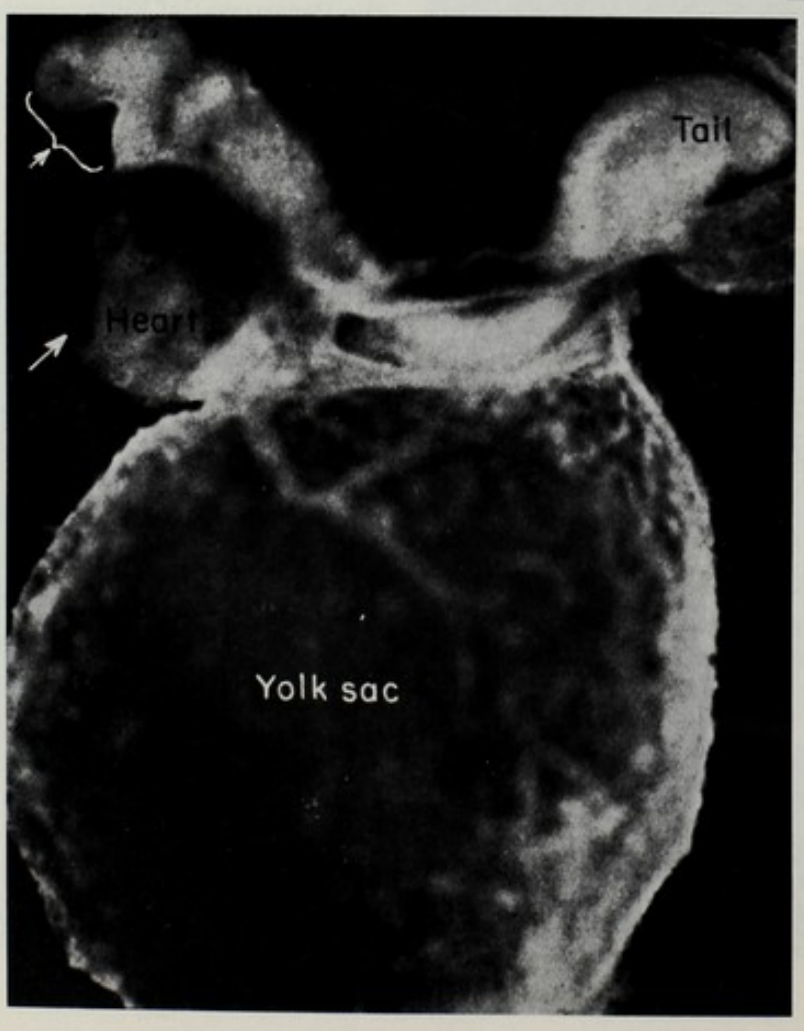


Figure 3.7. **Twenty-four days.** The fore part of the embryo is growing rapidly, especially the anterior neural plate. The cardiac tube, under the developing face (*arrow*), is functional.

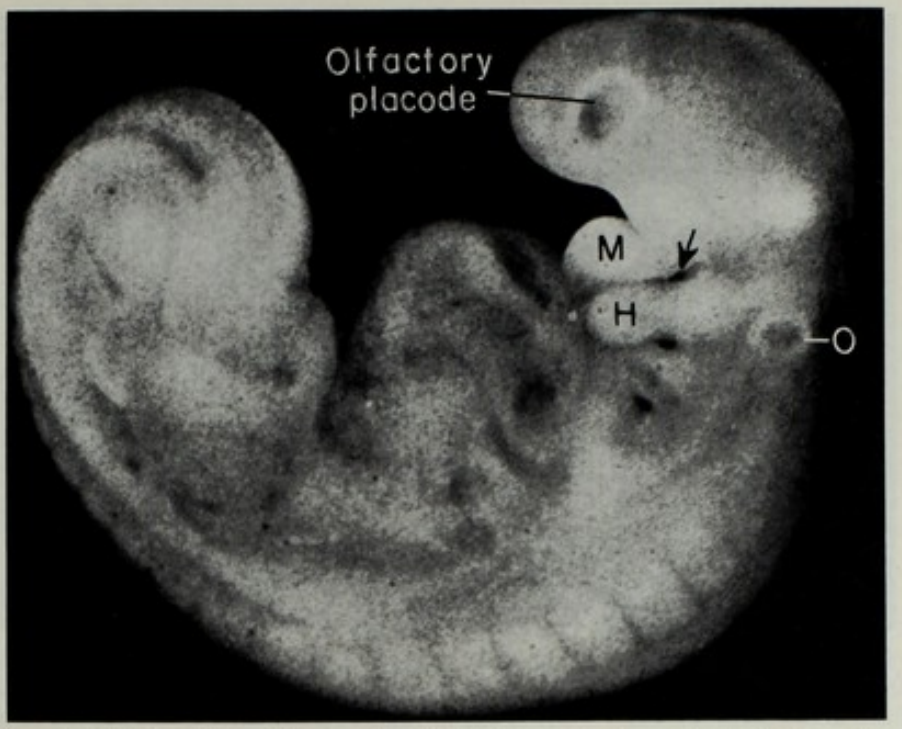


Figure 3.8. **Twenty-six days.** The olfactory placode has begun to invaginate. Between it and the mandibular process is the area of the future mouth, where the buccopharyngeal membrane, with no intervening mesoderm, is breaking down. Within the recess of the mandibular (M) and hyoid (H) processes the future external auditory canal will develop (*arrow*), and dorsal to it the otic placode (O) is invaginating to form the inner ear. The relatively huge heart must pump blood to the yolk sac and developing placenta as well as to the embryo proper. Foregut outpouchings and evaginations will now begin to form various glands and the lung and liver primordia. Foregut and hindgut are now clearly delineated from the yolk sac. The somites, which will differentiate into myotomes (musculature), dermotomes (subcutaneous tissue), and sclerotomes (vertebrae), are evident on into the tail, which will gradually regress.

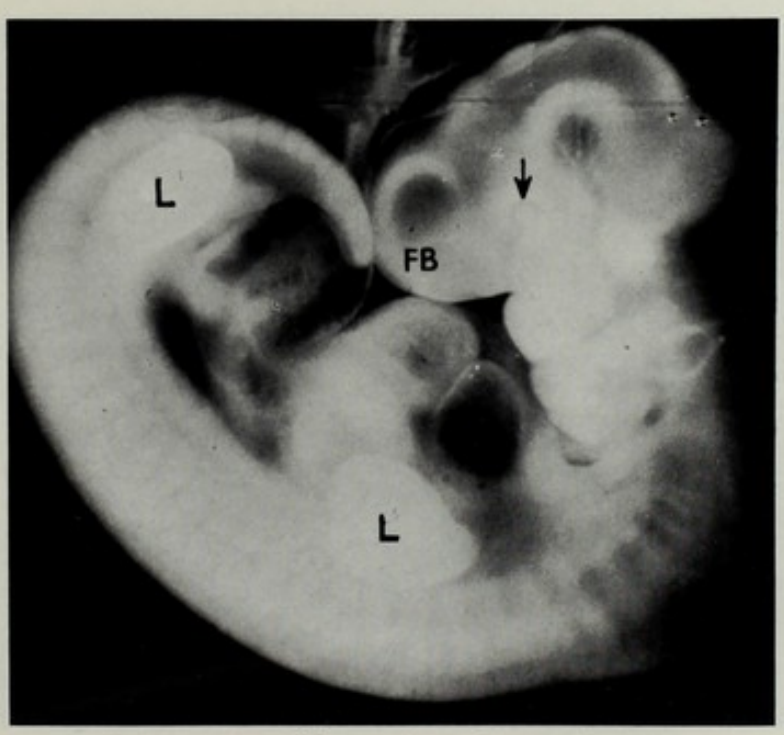


Figure 3.9. **Thirty days.** The brain is rapidly growing and its early cleavage into bilateral future cerebral hemispheres is evident in the telencephalic outpouching of the forebrain (FB). To the right of this is the developing eye with the cleft optic cup (*arrow*) and the early invagination of the future lens from surface ectoderm. From the somatopleura the limb swellings (L) have developed. The loose mesenchyme of the limb bud, interacting with the thickened ectodermal cells at its tip, carries all the potential for the full development of the limb. The liver is now functional and will be a source of blood cells. The mesonephric ducts, formed in the mesonephric ridges, communicate to the cloaca which is beginning to become septated, and the yolk sac is regressing.

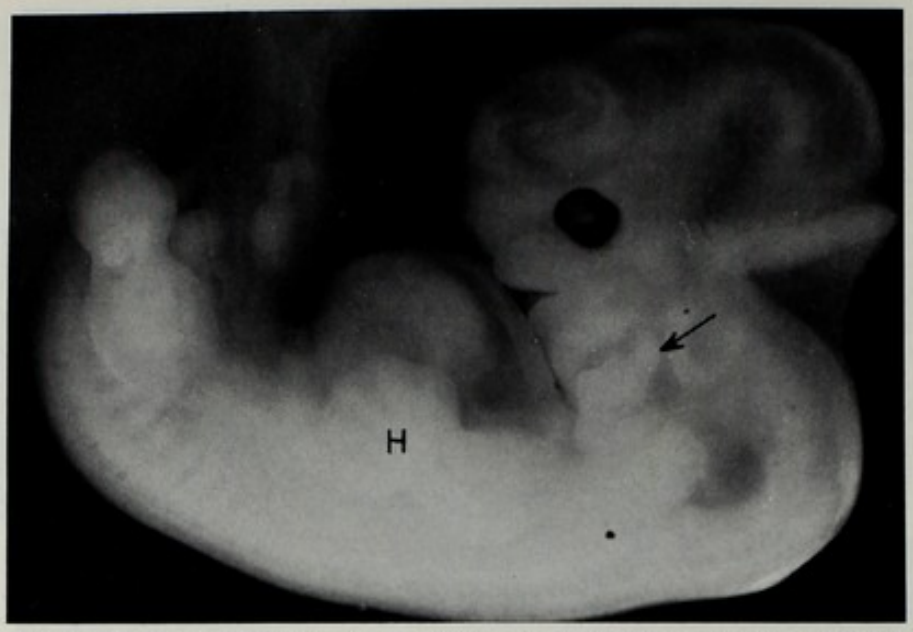


Figure 3.10. **Thirty-six days.** The retina is now pigmented, still incompletely closed at its inferior medial margin. Closure of the lip is nearly complete. The hillocks of His are forming the early auricle (*arrow*) from the adjacent borders of the mandibular and hyoid swellings. The hand plate (H) has formed with condensation of mesenchyme into the five finger rays. The lower limb lags behind the upper limb in its development. The ventricular septum is partitioning the heart. The ureteral bud from the mesonephric duct has induced a kidney from the mesonephric ridge, which is also forming gonad and adrenal. Cloacal septation is nearly complete, the infraumbilical mesenchyme has filled in all the cloacal membrane except the urogenital area, and the genital tubercles are fused whereas the labioscrotal swellings are unfused. The gut is enlongating, and a loop of it may be seen projecting out into the body stalk.

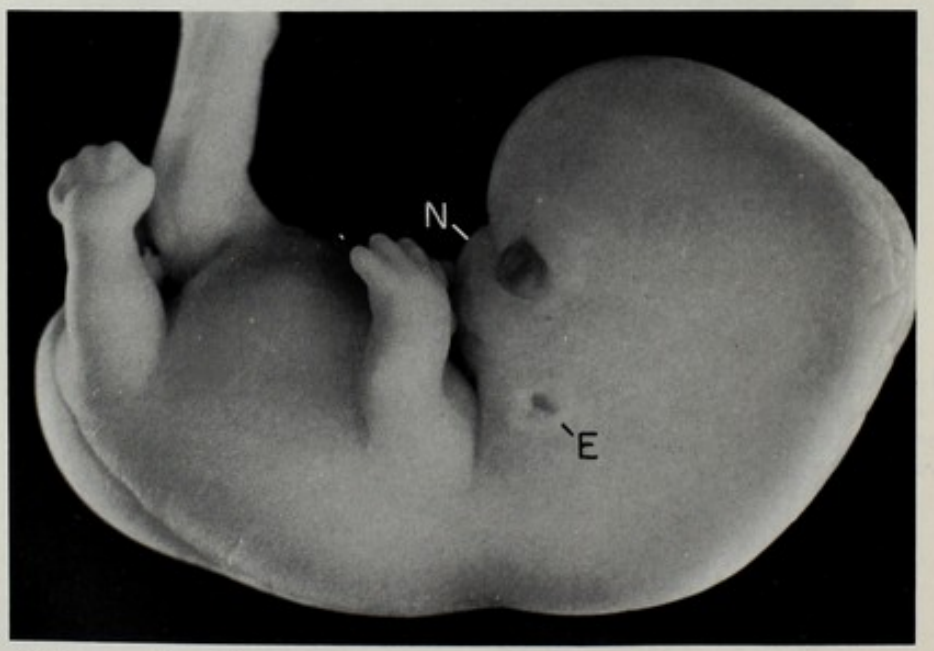


Figure 3.11. **Forty-one days.** The nose (N) is relatively flat, and the external ear (E) is gradually shifting in relative position as it continues to grow and develop. A neck area is now evident, the anterior body wall has formed, and the thorax and abdomen are separated by the transverse septum (diaphragm). The fingers are now partially separated, and the elbow is evident. The major period of cardiac morphogenesis and septation is complete. The urogenital membrane has now broken down, yielding a urethral opening. The phallus and lateral labioscrotal folds are the same for both sexes at this age. This is the end of the so-called embryonic period and the beginning of the fetal era.



Figure 3.12. **Ten week male.** The eyelids have developed and fused, not to reopen until four or five months. Muscles are developed and functional, normal morphogenesis of joints is dependent on movement, and primary ossification is occurring in the centers of developing bones. In the male the testicle has produced androgen and masculinized the external genitalia with enlargement of the genital tubercle, fusion of the labioscrotal folds into a scrotum, and closure of the labia minoral folds to form a penile urethra, these structures being unchanged in the female. The testicle does not descend into the scrotum until eight or nine months.



Figure 3.13. **Three and one half month male.** The fetus is settling down for the latter two thirds of prenatal life. The morphogenesis of the lung, largely solid at this point in development, will not have progressed to the capacity for aerobic exchange for another three to four months. The skin is increasing in thickness, and its accessory structures are differentiating. The form of the volar surface of the hand and foot, especially the character of the prominent apical and other pads, will influence the patterning of parallel dermal ridges which form transversely to the relative lines of growth stress on the palms and soles between 16 and 19 weeks. Subcutaneous tissue is thin, and adipose tissue does not develop until seven to eight months.

Table 3.1. Relative Timing and Developmental Pathology of Certain Malformations

TISSUES	MALFORMATION	DEFECT IN	CAUSE PRIOR TO	COMMENT
Central nervous system	Anencephaly	Closure of anterior neural tube	26 days	Subsequent degeneration of forebrain
	Meningomyelocele	Closure in a portion of the posterior neural tube	28 days	80% lumbosacral
Face	Cleft lip	Closure of lip	36 days	42% associated with cleft palate
	Cleft maxillary palate	Fusion of maxillary palatal shelves	10 weeks	
	Branchial sinus and/or cyst	Resolution of branchial cleft	8 weeks	Preauricular and along the line anterior to sternocleidomastoid
Gut	Esophageal atresia plus tracheoesophageal fistula	Lateral septation of foregut into trachea and foregut	30 days	
	Rectal atresia with fistula	Lateral septation of cloaca into rectum and urogenital sinus	6 weeks	
	Duodenal atresia	Recanalization of duodenum	7 to 8 weeks	
	Malrotation of gut	Rotation of intestinal loop so that cecum lies to right	10 weeks	Associated incomplete or aberrant mesenteric attachments
	Omphalocele	Return of midgut from yolk sac to abdomen	10 weeks	
	Meckel's diverticulum	Obliteration of vitelline duct	10 weeks	May contain gastric and/or pancreatic tissue
	Diaphragmatic hernia	Closure of pleuroperitoneal canal	6 weeks	
Genitourinary system	Extroversion of bladder	Migration of infraumbilical mesenchyme	30 days	Associated Müllerian and Wolffian duct defects
	Bicornuate uterus	Fusion of lower portion of Müllerian ducts	10 weeks	
	Hypospadias	Fusion of urethral folds (labia minora)	12 weeks	
	Cryptorchidism	Descent of testicle into scrotum	7 to 9 months	
Heart	Transposition of great vessels	Directional development of bulbus cordis septum	34 days	
	Ventricular septal defect	Closure of ventricular septum	6 weeks	
	Patent ductus arteriosus	Closure of ductus arteriosus	9 to 10 months	
Limb	Aplasia of radius	Genesis of radial bone	38 days	Often accompanied by other defects of radial side of distal limb
	Syndactyly, severe	Separation of digital rays	6 weeks	
Complex	Cyclopia, holoprosencephaly	Prechordal mesoderm development	23 days	Secondary defects of midface and forebrain
	Sirenomelia (sympodia)	Development of posterior axis	23 days	Associated defects of cloacal development

ABNORMAL MORPHOGENESIS

TYPES OF ABNORMAL MORPHOGENESIS

Structural anomalies can be divided crudely into several categories, each having somewhat different implications as to the type of error which occurred during morphogenesis.

Incomplete Morphogenesis

These are anomalies which represent incomplete stages in the development of a structure; they include the following subcategories, with one example listed for each:

Lack of development: renal agenesis secondary to failure of ureter formation.

Hypoplasia: micrognathia.

Incomplete separation: syndactyly (cutaneous).

Incomplete closure: cleft palate.

Incomplete septation: ventricular septal defect.

Incomplete migration of mesoderm: exstrophy of bladder.

Incomplete rotation: malrotation of the gut.

Incomplete resolution of early form: Meckel's diverticulum.

Persistence of earlier location: cryptorchidism.

Aberrant Form

An occasional anomaly may be interpreted as an aberrant form which never exists in any stage of normal morphogenesis. An example is the pelvic spur in the Nail-Patella syndrome. Such an anomaly may be more specific for a particular clinical syndrome entity than anomalies of incomplete morphogenesis.

Accessory Tissue

Accessory tissue—such as polydactyly, preauricular skin tags, and accessory spleens—all may be presumed to have been initiated around the same time as the normal tissue such as finger rays, auricular hillocks of His, and spleen, respectively.

Hamartomata

These anomalies represent an organizational defect leading to an abnormal admixture of tissues, often with a tumor-like excess of one or more tissues. Some have malignant potential. Examples of hamartomata are hemangiomata, melanomata, fibromata, lipomata, adenomata, and some strange admixtures that defy traditional classification.

Functional Defects

As an example, function is a necessary feature in joint development, and hence joint contractures such as club foot may result from functional deficit in use of the lower limb. Another potential clue toward defects of function of the limb may be derived from observing the creases of the hand. Creases on the palm or surface of the hand develop at planes of flexion of the early hand, and an anomaly such as early finger contracture (camptodactyly) will usually result in a lack of a crease at the nonfunctioning joint.

RELATIVE TIMING OF MALFORMATIONS

Malformations resulting from incomplete morphogenesis usually have their origin *prior to* the time when normal development would have proceeded beyond the form represented by the malformation. This type of developmental timing should not be construed as indicating that something happened *at* a particular time; all one can say is that a problem existed *prior to* a particular time.

Serious errors in early morphogenesis seldom allow for survival; hence only a few malformation problems are seen which can be said to have occurred prior to 23 days. Conjoined twins represent a partial to complete duplication of Hensen's node, the primitive streak, or both, and hence must have been initiated prior to 16 days. The cyclopia-cebocephaly type defect and the sirenomelia-sympodia type defect appear to be the consequence of defects in prechordal and postaxial mesoderm respectively, and presumably developed prior to 23 days. Aside from these examples, the vast majority of serious malformations represent errors that occur after three weeks of development.

Table 3.1 sets forth the relative timing as well as the presumed developmental error for some of the malformations which appear to represent incomplete stages in morphogenesis.

REFERENCES

1. Ebert, J. D.: Interacting Systems in Development. New York, Holt, Rinehart, and Winston, 1965.
2. Hamilton, W. J., Boyd, J. D., and Mossman, H. W.: Human Embryology. Baltimore, Williams and Wilkins Co., 1962.
3. Millen, J. W.: Timing of human congenital malformations. Dev. Med. Child. Neurol., *5*:343, 1963.
4. Nilsson, L., Ingelman-Sundberg, A., and Wirsen, C.: A Child Is Born. New York, Delacorte Press, 1965.
5. Streeter, G. L.: Developmental Horizons in Human Embryos; Age Groups XI to XXIII. Washington, D.C., Carnegie Institute of Washington, 1951.
6. Willis, R. A.: The Borderland of Embryology and Pathology. Washington, Butterworth, 1962.
7. Langman, J.: Medical Embryology. Baltimore, Williams and Wilkins Co., 1969.
8. Moore, K. L.: The Developing Human; Clinically Oriented Embryology. Philadelphia, W. B. Saunders Co., 1973.

Chapter Four

GENETICS, GENETIC COUNSELING, AND PREVENTION VIA EARLY FETAL RECOGNITION

relative to single defects and patterns of malformation

The basic process of morphogenesis is genetically controlled, being dependent on the environment for expression of the genetic potential.

Judging from the malformation problems for which a mode of etiology has been strongly indicated, the major cause is genetic aberration. There are three general genetic modes of determination for abnormal morphogenesis: polygenic determination, mutant genes in single or double dose, and gross genetic imbalance due to a chromosomal abnormality. Figure 4.1 provides a perspective as to the frequency of human disorders relative to each of these types of genetic determination. These are considered separately as they relate to problems of malformation, especially multiple defect syndromes. Recommended genetic counsel is presented at the end of each section.

POLYGENIC DETERMINATION

Much of the usual variability among individuals as well as many common disorders within a species may be ascribed to minor differences in a number of gene loci involved in the determination of a particular characteristic. A polygenically determined abnormality is herein defined as one that is predominantly the consequence of minor differences at many gene loci, no one of which may be held fully responsible for the abnormality. Obviously it is difficult to prove polygenic inheritance, but present evidence in the human indicates that this is the major mode in the etiology of many of the single localized defects in morphogenesis accounting for the majority of babies born with a malformation problem. The following indirect evidence for polygenic inheritance for the single common defects comes predominantly from the work of Carter[1] and has been partially summarized by Smith and Aase.[2]

1. Frequency of the Defect in Relatives

The frequency of *recurrence* for the same type of defect in offspring from unaffected parents ranges from 2 to 5 per cent (Table 4.1), 20 to 40 times the general frequency within that population group. The collected data are not compatible with autosomal dominant or recessive inheritance as being other than unusual modes of determination for such defects.

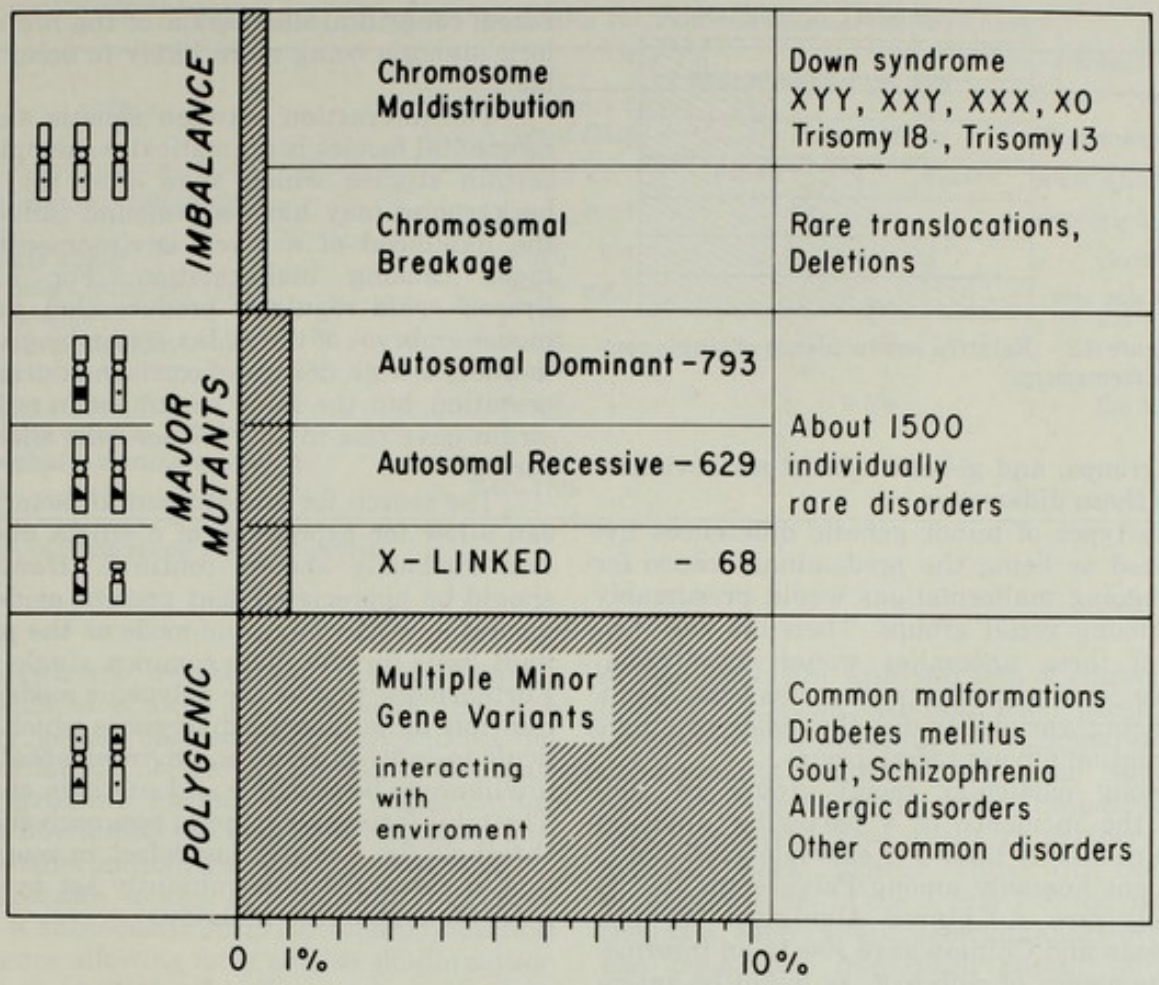


Figure 4.1. The scale at the base represents the percentage of individuals born who do have, or will have, a problem in life—secondary to a genetic difference. The three categories of genetic aberrations are depicted to the left. The dots within the chromosomes represent "normal" genes, the bar represents a dominant mutant gene, the hash-bar represents a recessive mutant gene, and the triangles denote minor gene variants.

2. Concordance in Twins

The question asked in these surveys is the following: if one twin has a defect, with what frequency does the other twin have the same type of defect? If both twins have the defect, they are concordant for the anomaly; if one twin has the defect and the other does not, they are nonconcordant. The incidence of concordance in nonidentical twins is of similar magnitude to that of siblings born of separate pregnancies and thereby gives no evidence toward a major environmental factor in the etiology for these defects. The frequency of concordance in identical twin sets is four to eight times the incidence in nonidentical twins, providing evidence for genetic factors in the etiology. Yet the highest concordance rate in identical twin sets, 40 per cent for cleft lip with or without cleft palate, amply demonstrates that given the same genetic background and similar intrauterine environment, the majority of identical twin sets are not concordant for these defects. This fact emphasizes the subtlety of the phenomena involved in the developmental pathology of these single localized defects in morphogenesis.

3. Influence of Genetic Background

a. Sex. The difference between the XX and the XY genetic background is one major genetic difference that has an appreciable effect on the occurrence of these major malformations, no one of which has an equal sex incidence (Fig. 4.2).

These sex differences provide cogent evidence for polygenic inheritance. Taking the example of pyloric stenosis, Carter[1] reasoned as follows: if it takes more genetic factors to give rise to this anomaly in the female, then the affected female should pass on more of these genetic factors to her offspring, who would have a higher frequency of pyloric stenosis than would the offspring of affected males. This is precisely what Carter found, the incidence of pyloric stenosis from affected mothers being four times as high as the incidence from affected fathers (24 per cent vs. 6 per cent). This is the type of quantitative effect that would be expected with polygenic inheritance.

b. Race. Numerous subtle genetic differences exist between racial groups. Persistent genetic isolation increases the differences be-

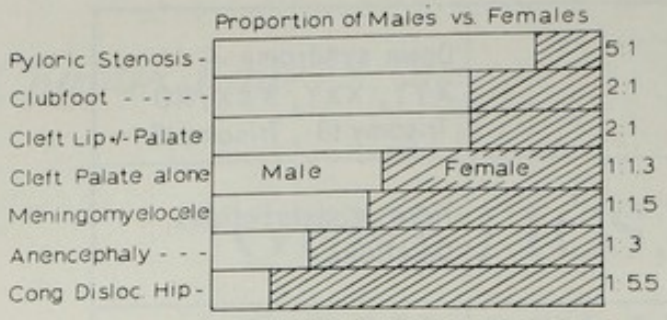


Figure 4.2. Relative sex incidence of single common malformations.

tween groups, and genetic admixture obviously lessens these differences.

The types of minor genetic differences hypothesized as being the predominant cause for the foregoing malformations would presumably differ among racial groups. Therefore the incidence of these anomalies would show racial variance. This is precisely what has been found, there being variability for the *types* of single malformation among racial groups.

Among particular racial groups or subgroups the incidence of a particular anomaly may be relatively high. For example, club foot is a frequent anomaly among Polynesians, but is relatively rare in Chinese. Admixture between Polynesian and Chinese gave rise to an intermediary frequency of club foot, as might be anticipated for polygenic inheritance.[5] Another similar example is polydactyly, which has an incidence of 0.7 per cent in Negroes, 0.24 per cent among the Caucasians, and 0.52 per cent among the mulatto racial admixture.[6]

4. Variation of Recurrence Risk in Relation to Severity of Malformation

In accordance with the hypothesis of polygenic inheritance for the foregoing anomalies, the more severe the degree of malformation, the greater the adverse genetic influences involved and thereby the greater should be the chance for recurrence from the same parentage. Carter[1] has obtained data which support this hypothesis. The risk for recurrence in subsequent children when an offspring has a severe bilateral cleft lip and palate is 5.7 per cent, as contrasted to a 2.5 per cent recurrence risk when the offspring has a less severe degree, a unilateral cleft lip.

INTERACTION BETWEEN GENETIC AND ENVIRONMENTAL FACTORS

Environmental influences can play a role in determination of these malformations. Some indications of environmental effects have been observed in Scotland and England in studies of anencephaly-meningomyelocele families, namely, seasonal variability[7] and social class differences.[8] Birth order influences have also been noted, congenital dislocation of the hip and pyloric stenosis being more likely to occur in first born.[1]

The interaction between genetic and environmental factors is dramatically exemplified by certain studies which show that the genetic background may have a profound influence on the likelihood of a given environmental teratogen causing malformation. For example, Fraser[9] could regularly produce cleft palate in mouse embryos of the A/Jax strain by giving the mothers a high dosage of cortisone during early gestation, but the same treatment in a different strain gave rise to only 17 per cent affected offspring.

The search for environmental factors which can allow for expression of a single malformation obviously should continue. However, it should be appreciated that present evidence indicates a subtle polygenic mode as the predominant basis for the more common single defects. Furthermore, just as the polygenic mode implies multiple minor genetic differences which are difficult to individualize, so environmental factors are likely to be multiple and subtle in character. The total factors combine to approach the subtle threshold for a particular defect in morphogenesis, a threshold predominantly set by the genetic makeup of the individual.

Counsel for Defects for Which Polygenic Inheritance Has Been Indicated

1. Explain the developmental pathology of the defect so that the parents can appreciate that there was only a single localized defect in the early development of their child. Then discuss the management and prognosis for the child. When the single defect is of the type which – with repair – need not interfere with the social acceptance or function of the child, it is often helpful to tell the parents that the *child* is normal. For example, given a child with isolated cleft lip, the parents may be told, "Your *child* is normal; the *lip* did not close completely, and therefore we shall have a plastic surgeon bring about the closure." The purpose of this approach is to assist in the parental acceptance of the child by not branding the whole child as malformed, but localizing the defect to what it actually represents in an anatomical and functional sense.

2. Explain that the localized problem in development must have occurred *prior to* a particular time in gestation (see Table 3.1 p. 414), and reassure the parents that it was not related to any factor after that time.

3. Ask the parents if they have any ideas concerning the cause of the malformation. Many of the parental concerns relative to etiology can be dispelled.

4. Explain that morphogenesis is a genetically determined process in which numerous

Table 4.1. Recurrence Risks for Some Single Defects[1–4]

DEFECT	RECURRENCE RISK FOR		
	Normal Parents of One Affected Child	*Future Males*	*Future Females*
Cleft lip with or without cleft palate	4–5%*		
Cleft palate alone	2–6%		
Cardiac defect (common types)	3–4%		
Pyloric stenosis	3%	4%	2.4%
Hirschsprung anomaly	3–5%		
Club foot	2–8%		
Dislocation of hip	3–4%	0.5%	6.3%
Neural tube defects—anencephaly, meningomyelocele	3–5%		
Scoliosis	10–15%		

*Range of recurrence risks observed.

genes play a role, as a team, in the development of a given structure. Then indicate that the "team of genes" derived from *both* parents did not allow for full normal development of the particular structure leading to the malformation. Indicate how subtle the end point is, toward normal or malformation, for such single defects.

5. Indicate to the parents that the likelihood of a subsequent offspring having a similar set of genes allowing for a similar malformation is of low magnitude, 3 to 5 per cent or less for most of the single common defects with the exception of scoliosis. The more precise recurrence risk data are summarized in Table 4.1. In giving this counsel the risk figures may be mildly increased when the defect is severe in degree and decreased when the anomaly is mild in degree. The risk figures may be separately stated for the sex of the offspring, especially for pyloric stenosis and congenital dislocation of the hip. If two offspring are affected, the risk for subsequent offspring being affected is two- to three-fold greater than the previously mentioned figure, around 10 to 15 per cent. The risk of an affected individual having affected offspring is of similar magnitude to that of the sibling recurrence risk, around 3 to 5 per cent.

Note: This counsel is obviously crude, being based on empiric data. However, to the author it seems the most appropriate at our present state of knowledge and is thereby preferable to not giving the parents any perspective on etiology and recurrence risk. Hopefully future knowledge will allow for more precise counseling relative to individuals with a single localized malformation.

MAJOR MUTANT GENE DETERMINATION

Genes located in the X chromosome are referred to as X-linked genes and those on the autosomes as autosomal-linked genes. Man is a diploid organism with two sets of chromosomes, one set being derived from each parent. Each pair of chromosomes will have comparable gene determinants located at the same position on each chromosome of the pair. The pair of genes may be referred to as *alleles*, or partners, which normally work together. Thus, with the exception of the genes of the X and Y chromosomes in the male, each genetic determinant is present in *two doses*, one from each parent. A *mutant* gene indicates a *changed* gene. A major mutant gene is herein defined as a genetic determinant which has changed in such a way that it can give rise to an abnormal characteristic. If a mutant gene in single dose gives rise to an abnormal characteristic despite the presence of a normal allele (partner), then it may be referred to as *dominant* because it causes abnormality even when counterbalanced by a normal gene partner. A mutant gene which only causes an abnormal characteristic when present in double dosage (or single dosage without a normal partner, as for an X-linked mutant gene in the male) is referred to as recessive. There are gradations from a mutant gene that always causes an abnormal characteristic in single dosage (dominant), to one which occasionally causes some abnormality in single dosage (semidominant), to one that never causes any evident alteration except when present in double dosage (recessive). These principles are set forth in Figure 4.3.

Expression is a term used to indicate the extent of abnormality that is due to a genetic aberration. The expression may be stated as severe, usual, mild, or no expression, the latter being synonymous with lack of penetrance in an individual who has the genetic aberration. Individuals with the same genetic aberration frequently show variance in expression, especially with respect to malformations.

Traditionally, the mutant gene disorders have been categorized into those due to genes

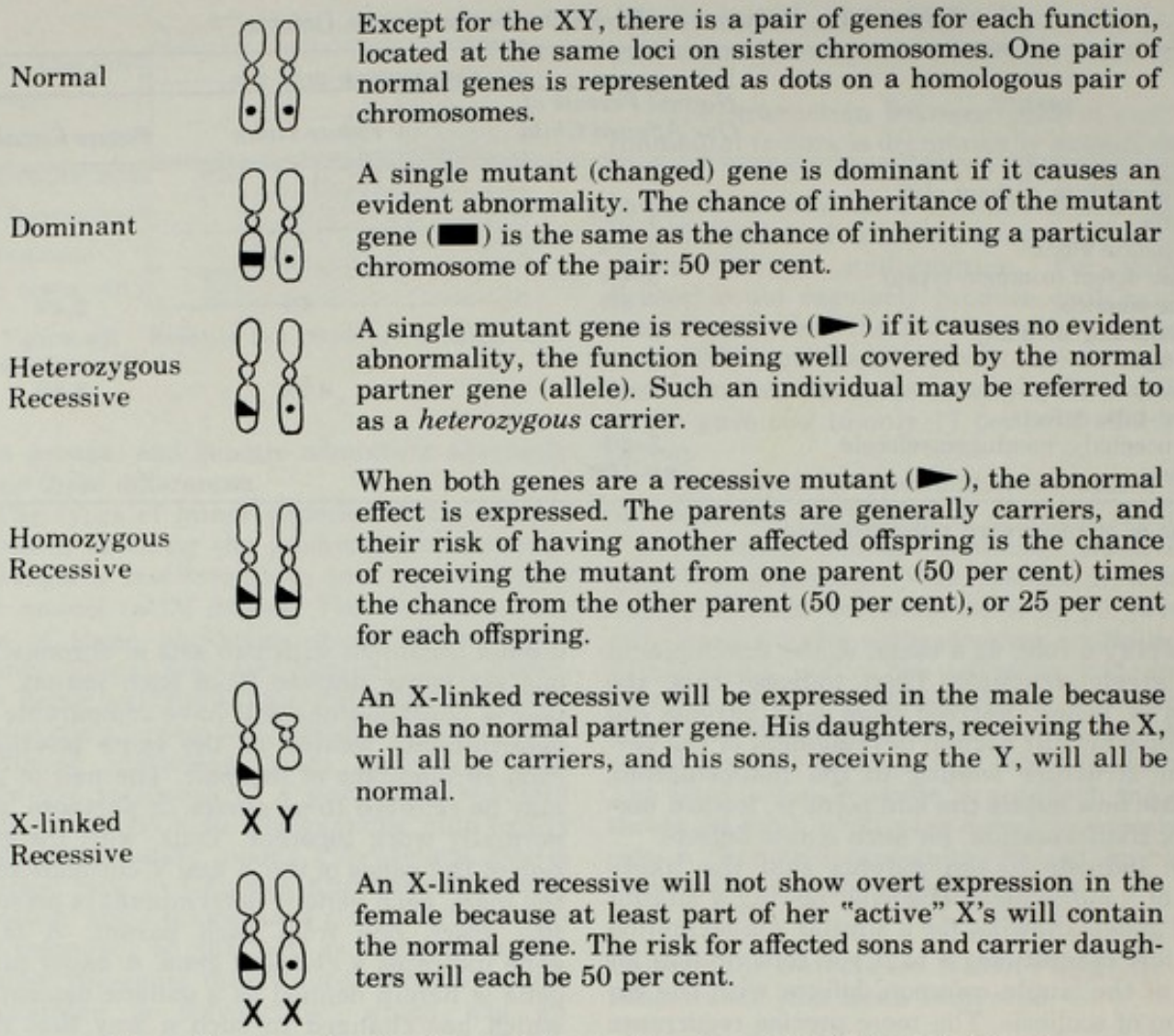


Figure 4.3. Normal and major mutant gene inheritance (Mendelian inheritance).

located on the autosomes—autosomal dominant and autosomal recessive—and disorders due to genes on the X-chromosome—X-linked recessive and X-linked dominant.

AUTOSOMAL DOMINANT

Autosomal dominant disorders often show wide variation in expression among affected individuals, presumably because of minor differences in the normal allele (partner) of the mutant gene as well as other differences in the genetic or environmental background of the affected individual. Figure 4.4 demonstrates the variance in expression for an autosomal dominant disorder, ectrodactyly. The risk of the single mutant gene being passed to a given offspring is 50 per cent, yet the risk of a severe defect of hand development is less than 50 per cent because of variance in expression. To utilize the example of the Waardenburg syndrome, the risk of inheritance of the mutant gene from an affected individual is 50 per cent, yet only about 20 per cent of affected individuals have deafness, the most disturbing expression of the mutant gene. Hence the risk for deafness in offspring of a parent with the Waardenburg syndrome is the risk of receiving the mutant gene (50 per cent) times the likelihood of expression for deafness in the disorder (20 per cent), or 10 per cent. This dichotomy between the risk of receiving the gene and the risk of a particular expression of the disorder must be utilized in counseling, especially for autosomal dominant disorders.

The first question to ask oneself after making the clinical diagnosis of an autosomal dominant mutant gene disorder is: "When did the gene mutation occur?" If the disorder is one which always shows some expression and the parents are quite normal, then this may be presumed to be a *fresh gene mutation* which happened in one of the germ cells that went to form the conceptus. The parents of a child who has a fresh gene mutation therefore have a negligible risk for recurrence. Actually a high proportion of individuals with autosomal dominant patterns of malformation represent fresh gene mutations. Since the affected individuals often have limited capability of reproduction, the majority of cases seen are fresh mutations. For some conditions such as the Apert syndrome there have been only a few reported cases of offspring from affected in-

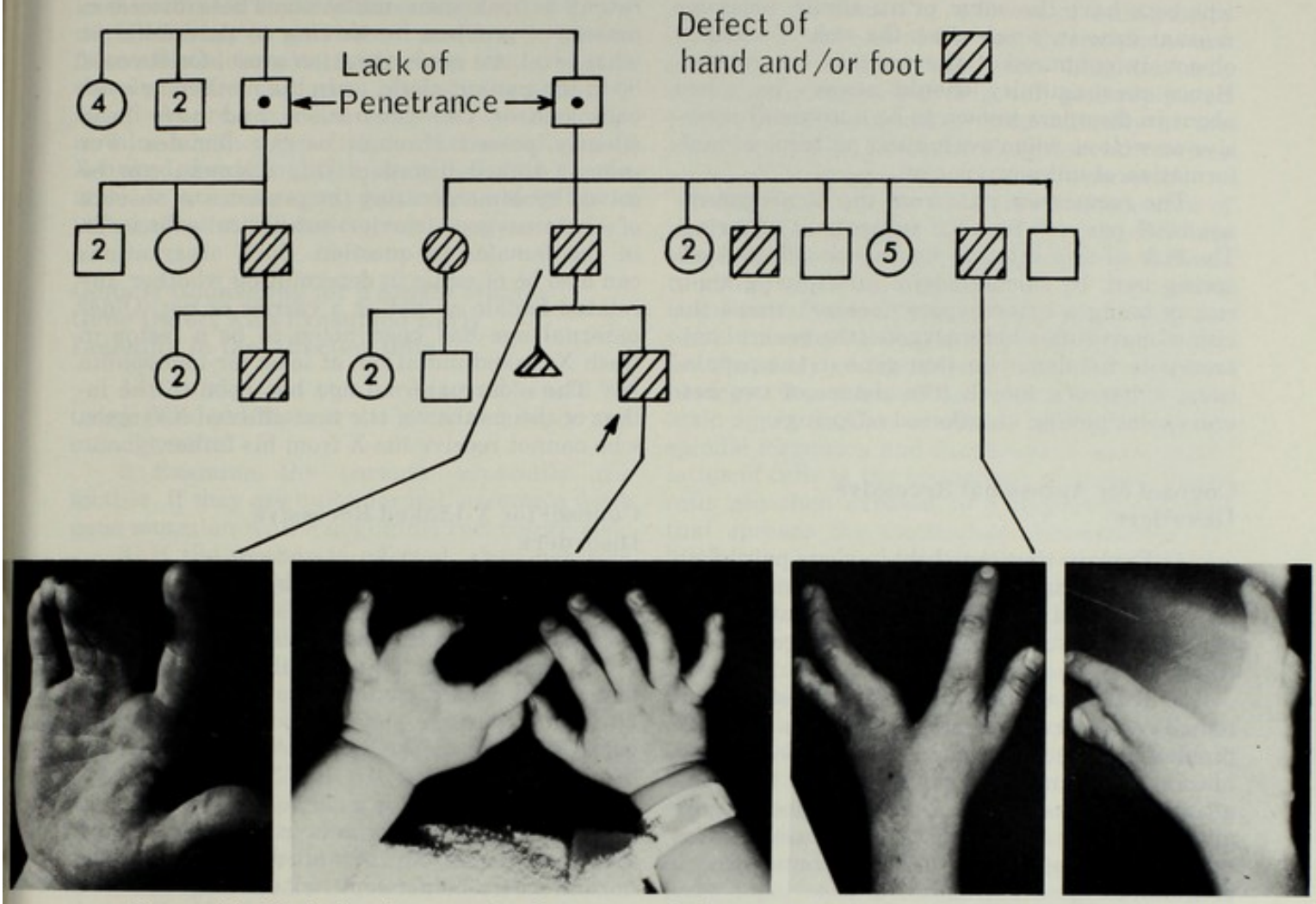


Figure 4.4. Variation in expression for autosomal dominant ectrodactyly among various related individuals. Note also the *intra-individual* asymmetry of expression in the propositus (*arrow*). (From Smith, D. W.: J. Pediatr., *69*:1150, 1966.)

dividuals, but these demonstrated the autosomal dominant inheritance. Some of the sporadic syndromes of unknown etiology may also be single gene mutations, but lack of reproduction prevents a testing of the hypothesis. Fresh gene mutation is more likely at *older paternal age*, as has been shown for at least 12 autosomal dominant syndromes of malformation.[10] Hence paternal age should always be noted in the evaluation of disorders which may be the consequence of a single mutant gene.

Counseling for Autosomal Dominant Disorders

1. Examine the parents and siblings and occasionally other relatives to determine whether any of them show features of the disorder in question. If neither parent shows any expression of an autosomal dominant disorder, which always shows some effect on the individual, the parents may be told, "A single gene was altered in one of the germ cells prior to the development of the child. This event is extremely unlikely to happen again, and therefore your risk for further affected children is negligible." They should also be reassured that relatives need have no concern of having affected children.

2. The risk for an *affected* individual having an affected child is 50 per cent for each offspring. When possible, be acquainted with the frequency of various features in affected individuals so the counsel can include not only the risk of a given offspring receiving the mutant gene but also the likelihood of any particular defect occurring.

3. Explain, when feasible, the developmental pathology and how all the aspects of altered development are secondary to the effects of the single altered gene. Outline the natural history of the condition and management for the child.

AUTOSOMAL RECESSIVE

Autosomal recessive disorders generally have less variation in expression than do autosomal dominant syndromes. Possibly this is because both genes of a pair are mutant, and therefore there is *no* normal partner gene to carry on the function of the particular gene. The inheritance is from clinically normal parents

who both have the *same*, or an allelic, recessive mutant gene in *single dose*, the risk of which is obviously enhanced if the parents are related. Hence consanguinity should always be asked about in disorders known to be autosomal recessive as well as when evaluating patterns of malformation of unknown cause.

The recurrence risk from the same parentage is 25 per cent for each subsequent offspring. The risk of any relative having an affected offspring may be calculated by multiplying their risk of being a heterozygote (carrier), times the risk of marrying a heterozygote (the general heterozygote frequency for that gene in the population), times one fourth (the chance of two heterozygotes having an affected offspring).

Counsel for Autosomal Recessive Disorders

1. Explain that the child has one pair of altered genes and that the disturbance in development is caused by that pair of altered genes. Outline the natural history and management for the child.

2. Explain to the parents that most individuals have several altered genes which cause no problem because each is counterbalanced by its normal gene partner. They happen to have one altered gene in common, and the chance of any given offspring receiving both of these altered genes and being affected is 25 per cent for each pregnancy.

3. Explain that the chance of their normal children having a single altered gene (carrier) is two out of three, but since the chance of randomly marrying another carrier is small their risk of having affected children should be quite small. The general risk of any unaffected relative having an affected child may be calculated, as set forth above.

X-Linked Recessive

The X-linked genes in the XY male are present in but a single dose with no partner gene in the male, and hence the full recessive disorder is expressed with but a single recessive mutant gene. The frequency of X-linked recessive disease in the male is thereby a direct reflection of the frequency of X-linked recessive genes per X chromosomes in the population. The chance of an XX female having a pair of such X-linked recessive genes and expressing the same disorder as the male is very small. Hence the following precepts are the important ones in detecting X-linked recessive inheritance:

1. With rare exception only males are affected and the transmission is through unaffected heterozygous (carrier) females.

2. There is no male transmission.

X-linked recessive disorders in the male, especially the more severe ones, may often represent a fresh gene mutation. These disorders present a problem in striving to determine at what level the gene mutation arose, for it could be in the patient alone, or in the mother, or even back one or two generations and have been silently passed through carrier females. For some X-linked disorders this dilemma can be solved by demonstrating the presence or absence of a heterozygous (carrier) subclinical expression in the females in question. Such observations can also be of value in determining whether any related female at risk is a carrier or not. Older paternal age has been noted to be a factor in fresh X-linked mutation, at least for hemophilia A.[11] The older paternal age has been in the father of the mother of the first affected XY male, who cannot receive his X from his father.

Counsel for X-Linked Recessive Disorders

1. First, try to determine by family pedigree evaluation, or observation of heterozygous expression, whether the mother is a carrier or not.

2. Explain the X-linked single mutant gene and how it caused trouble because the male has no normal partner gene to counter the mutant gene. Then relate the natural history and management for the boy.

3. If the mother is a carrier she may be told that there is a 50 per cent risk of any future male being affected; that all daughters will be normal with a 50 per cent risk of being a carrier; that normal sons cannot transmit the disorder; and that affected sons would have normal sons who cannot transmit the disease, and all their daughters would be unaffected carriers.

4. If the mother is *not* a carrier, then the risk for recurrence from the mother is negligible and the affected boy's risk is as listed above.

X-Linked Dominant

X-linked single gene *dominant* disorders show expression in the XX female, usually with a more severe effect in the XY male. This type of inheritance is most commonly confused with autosomal dominant inheritance from which it may be discriminated in the following ways:

1. There is usually a more severe expression in affected males.

2. Affected males have normal sons (no male to male transmission) and all their daughters are affected.

The counseling is the same as for X-linked recessive except that all carrier females are affected.

Single Mutant Gene With Sex Limitation

Several disorders, such as the oral-facial-digital syndrome, are found almost exclusively in females and apparently cause early lethality

in the affected male because there is a 50 per cent deficiency in sons as compared to daughters from affected females, with about 50 per cent of the daughters and none of the sons being affected. At present it has not been possible to determine whether this disorder, for example, is an X-linked dominant with early lethality in the male or an autosomal dominant which has a lethal effect in the male.

Genetic Counseling for a Single Mutant Gene Defect with Presumed Early Lethality in the Affected Male

1. Explain that this is due to a single altered gene and discuss the natural history and management.
2. Examine the parents, especially the mother. If they are quite normal, assume a fresh gene mutation with a negligible recurrence risk.
3. If the mother is affected, then her risk would be one in three for a normal male, one in three for an affected female, and one in three for a normal female. The same risks would apply for any affected female.

GENETIC IMBALANCE DUE TO GROSS CHROMOSOMAL ABNORMALITIES

The 46 normal chromosomes consist of 22 homologous pairs of autosomes plus the XX pair of sex chromosomes in the female and the XY in the male. Normal development is not only dependent on the gene content of these chromosomes, but on the gene balance as well. An altered number of chromosomes most commonly arises because of a fault in chromosome distribution at cell division. During the gametic meiotic reduction division (Fig. 4.5) one of each pair of autosomes and one of the sex chromosomes are distributed randomly to each daughter cell, whereas during mitosis (Fig. 4.6) each replicated chromosome is separated longitudinally at the centromere such that each daughter cell receives an identical complement of genetic material.

Figure 4.7 shows the natural appearance of stained chromosomes at early, mid, and late stages of mitosis. It would obviously be difficult to count these chromosomes or to distinguish their individual structure from such preparations. In order to obtain adequate preparations for the study of chromosome number and morphology, the cultured cells are treated with a toxic agent such as colchicine which blocks the spindle formation and thus leads to the accumulation of cells at the metaphase of mitosis. These cells are then exposed to a hypotonic solution that spreads the unattached chromosomes, allowing for such preparations as that shown in Figure 4.8. Various techniques can be employed to allow for the identification of individual chromosomes. For example, trypsin treatment and Giemsa staining bring out the banding patterns in chromosomes, as shown in Figure 4.8.

Abnormal morphogenesis may result from genetic imbalance. Figure 4.9 illustrates some of the types of chromosomal abnormalities which can lead to gross genetic imbalance.

Chromosomal maldistribution leading to an altered number of chromosomes occurs in at least 4 per cent of recognized pregnancies (see Fig. 4.10). Most of the genetic imbalances have such an adverse effect on morphogenesis that the conceptuses do not survive. Figure 4.10 summarizes the frequency and types of chromosomal abnormalities found in spontaneous abortuses, about 50 per cent of which have a chromosomal

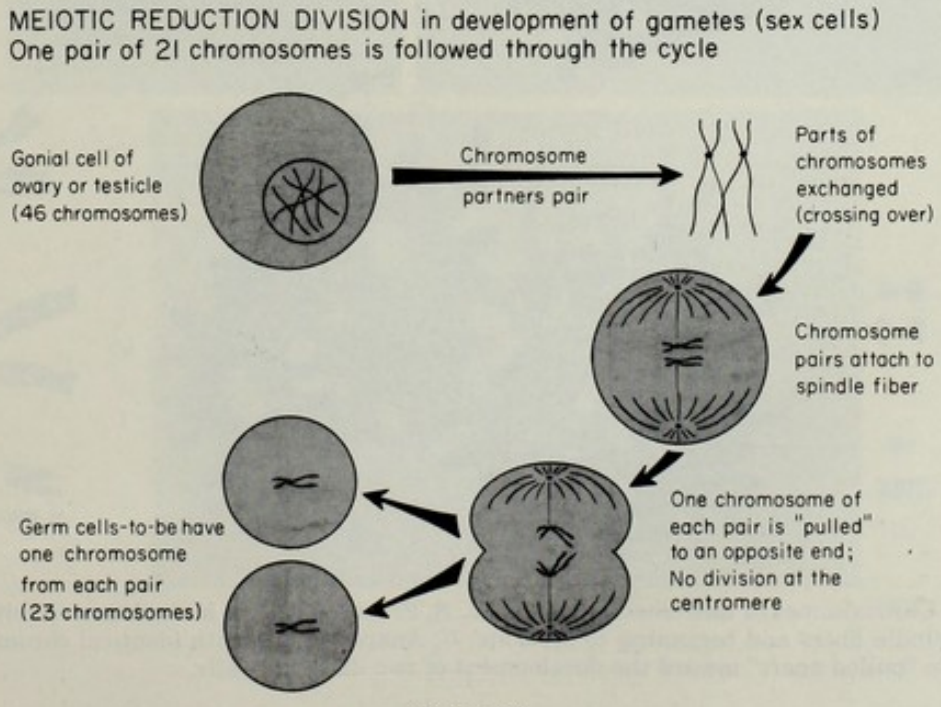


Figure 4.5.

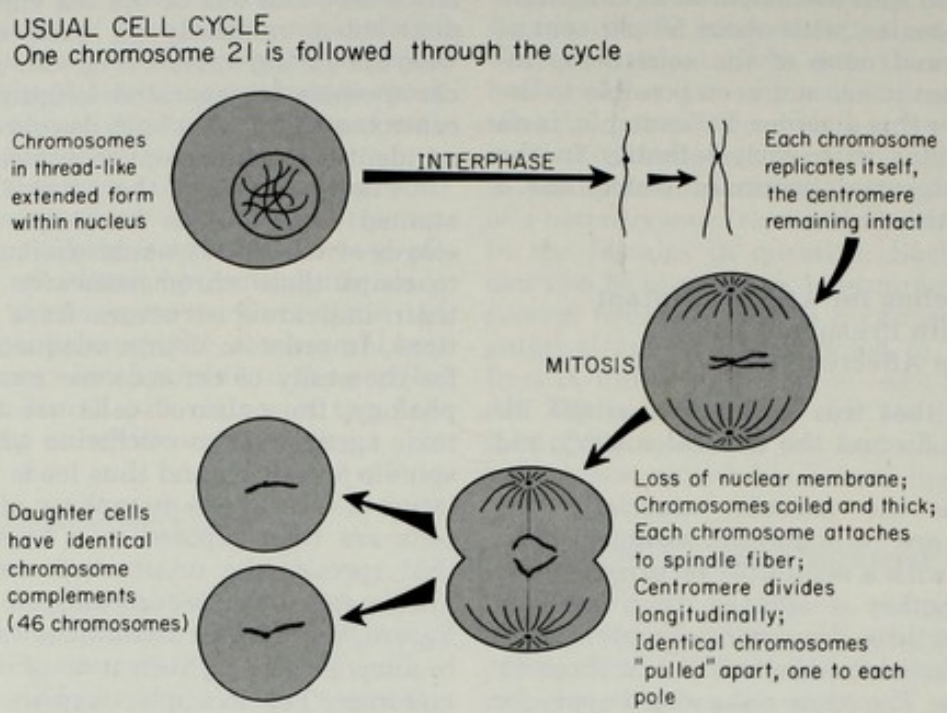


Figure 4.6.

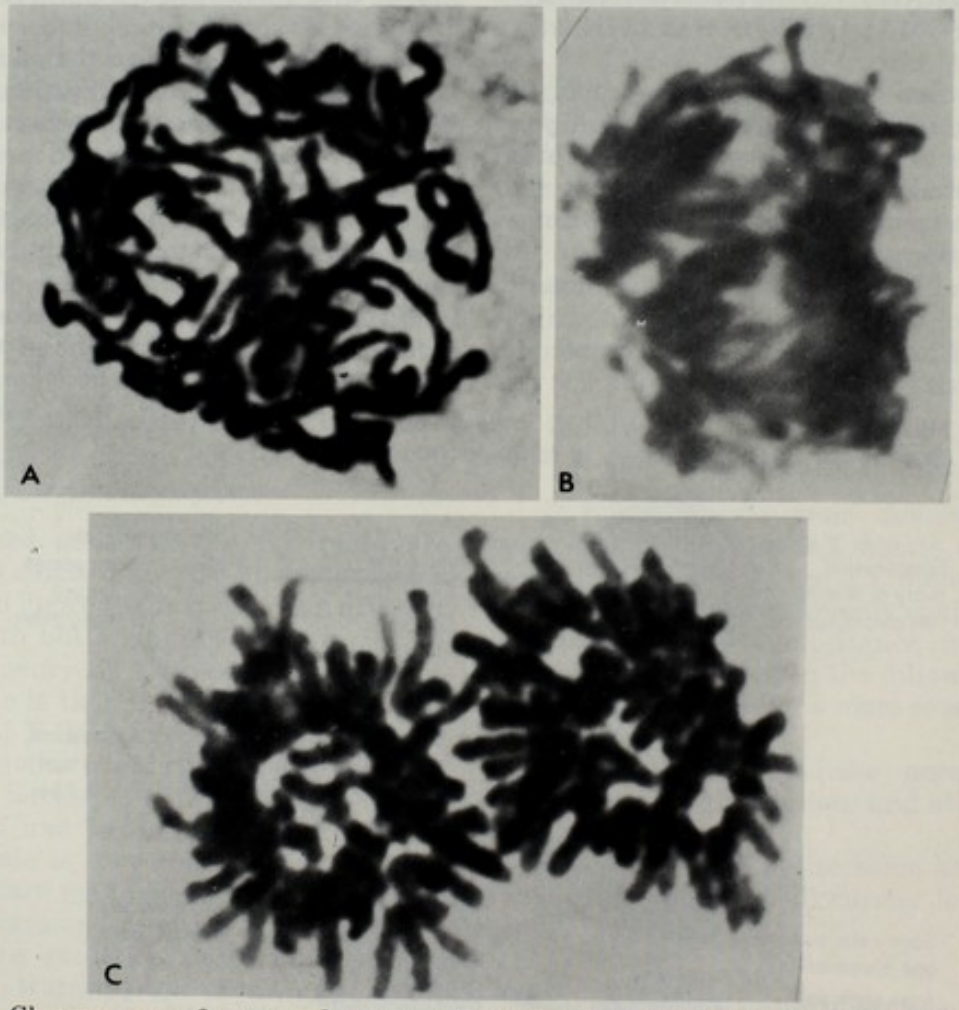


Figure 4.7. Chromosomes of untreated mitotic cells. *A*, Prophase cell. *B*, Metaphase cell with chromosomes attached to the spindle fibers and beginning to separate. *C*, Anaphase cell, with identical chromosomal complements having been "pulled apart" toward the development of two daughter cells.

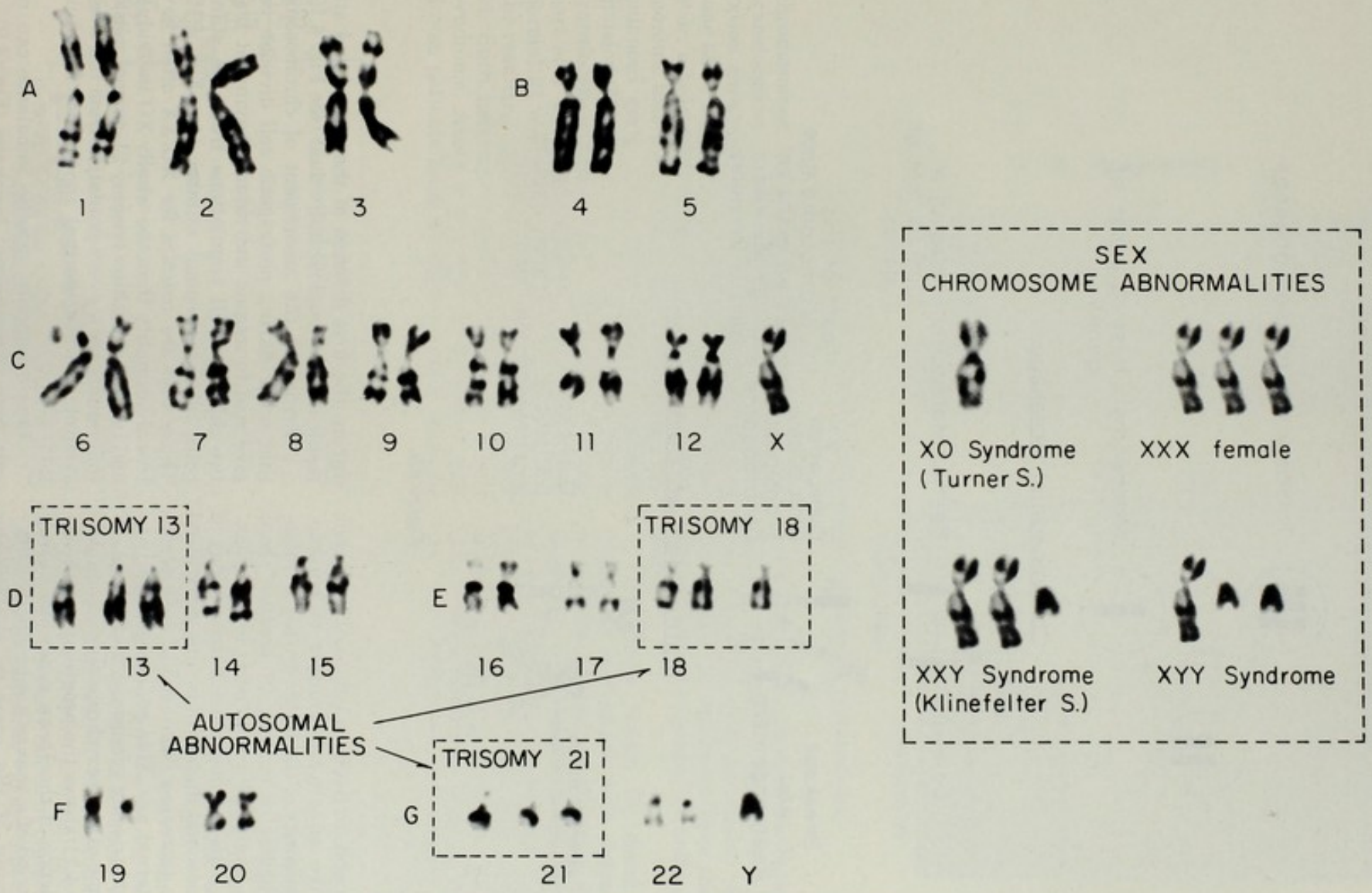


Figure 4.8. Giemsa-stained chromosomes arranged into a karyotype by letter grouping and number designation on the basis of length of the chromosome, position of the centromere, and banding patterns. The common types of aneuploidy in newborn babies are shown within the boxes.

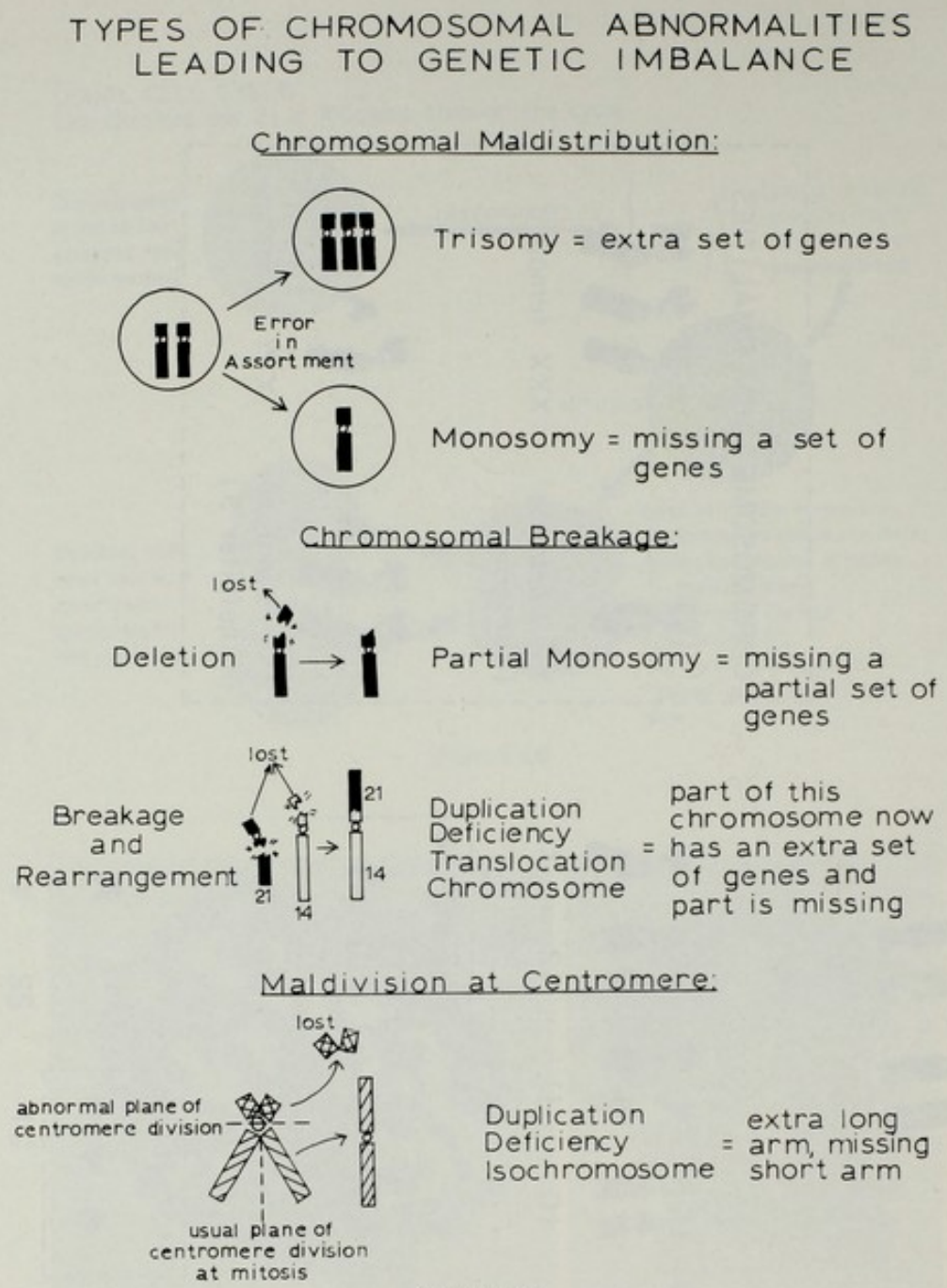


Figure 4.9.

abnormality and, in liveborn babies, 0.5 per cent of whom have an altered number of chromosomes. The majority of the latter are sex chromosome aneuploidies or trisomy 21 because these are the least likely to have an early lethal effect.

Though little is known about the etiology of faulty chromosomal distribution, one recognized factor is the increased likelihood of such errors at older maternal age. This applies especially to the autosomal trisomy syndromes and to a lesser extent to some of the sex chromosome aneuploidies. Figure 4.11 shows the progressive increase in the frequency of the Down syndrome during the latter period of a woman's reproductive life.

The timing of the error in chromosome distribution seldom can be stated with assurance, for it could occur prior to meiosis, during the first or second divisions of meiosis, or even during the first division of the zygote and still result in an aneuploid individual (see Fig. 4.12).

Errors in the assortment of chromosomes that occur during postzygotic cell division can give rise to mosaic individuals having at least two different cell populations from the standpoint of chromosomal number (see Fig. 4.12). Those who are mosaics for XO/XX often have less abnormality than the wholly XO individual, and in similar fashion trisomy 21-normal mosaic individuals show every gradation from the Down syndrome to near-normal appearance and function.

Less commonly, genetic imbalance can result from chromosomal breakage (Fig. 4.9). A broken piece of a chromosome may be lost. With more than one break, rearrangement of chromosomal pieces may take place between the broken

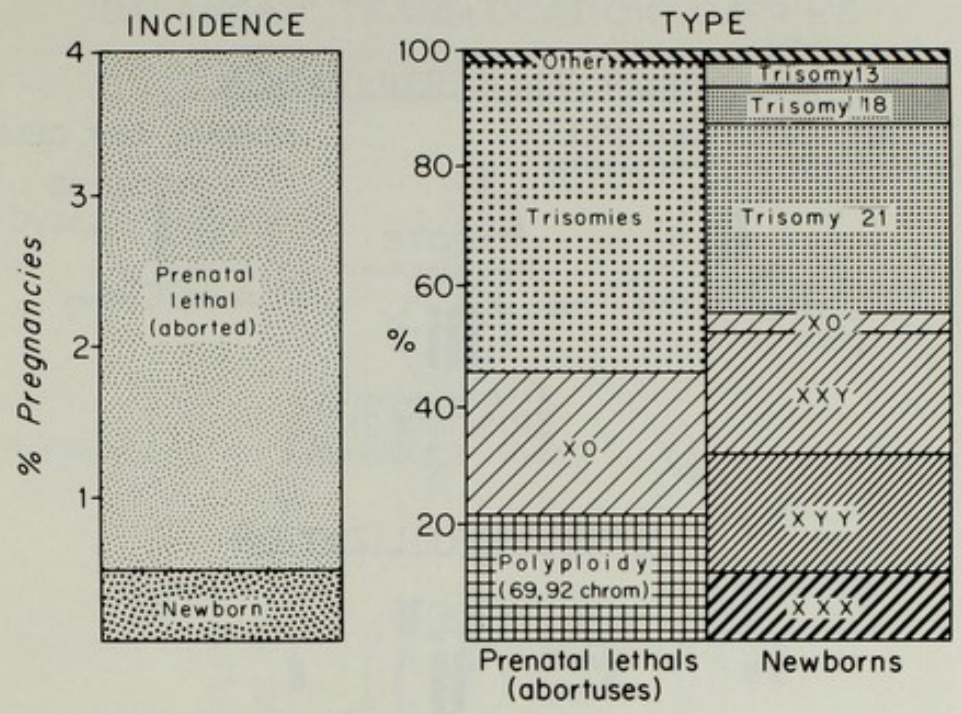


Figure 4.10. Incidence and types of chromosomal abnormalities.

chromosomes, a phenomenon referred to as translocation. An individual can have a translocation chromosome with no evident problem as long as he still has a balanced set of genes. However, a balanced carrier of a translocation chromosome has a significant risk of producing unbalanced germ cells during meiotic reduction division (Fig. 4.13). Should a germ cell receive a translocation chromosome containing a large part of a 21 chromosome and also receive the normal 21 chromosome from that same parent, the resulting zygote would have partial trisomy 21. Such individuals generally have the Down syndrome. About 6 per cent of the Down syndrome patients have 46 chromosomes, with the extra dose of 21 chromosome being attached to another chromosome. Similarly, a small proportion of patients with the trisomy 18 syndrome or the trisomy 13 syndrome have the extra set of genes attached as part of a translocation chromosome.

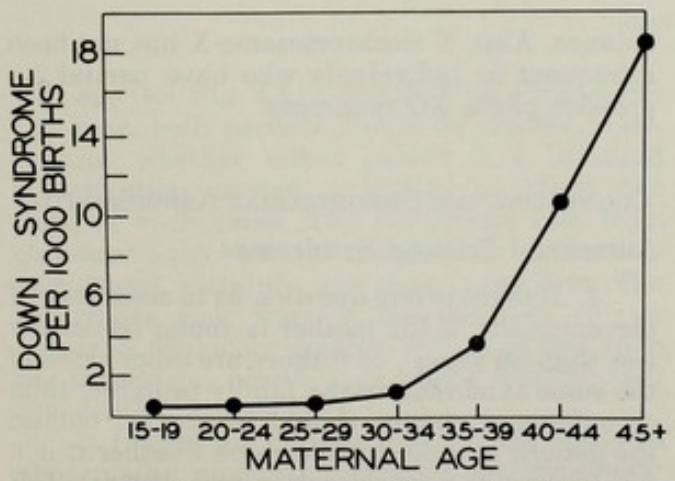


Figure 4.11. Increasing incidence of the Down syndrome during the latter period of a woman's reproductive period. (From Smith, D. W.: Am. J. Obstet. Gynecol., *90*:1055, 1964.)

The major reason for doing chromosome studies on individuals with autosomal trisomy syndromes, beyond confirmation of the clinical diagnosis, is to determine whether the patient has a translocation chromosome rather than the more usual full trisomy. This applies predominantly to babies with genetic imbalance disorders who are born to younger mothers, since the vast majority of such babies born to older mothers have full trisomy. If it is a translocation case, then both parents should be studied to determine whether either of them is a balanced translocation carrier with a consequent high risk of having affected offspring. Fortunately only about one third of the patients with partial translocation trisomy will be found to have a translocation carrier parent, because most of them represent fresh occurrences for which there is a negligible recurrence risk.

Chromosomal breakage with or without rearrangement allows for a wide variety of individually rare genetic imbalances with extra or missing segments of chromosomes. Many of these do not survive prenatal life. Among undiagnosed mentally deficient children with multiple defects Summitt[12] found 8 per cent to have a chromosomal abnormality, most of whom had a small extra piece of autosome and/or a piece missing. Our own experience with 145 such unknown multiple defect cases revealed three (2 per

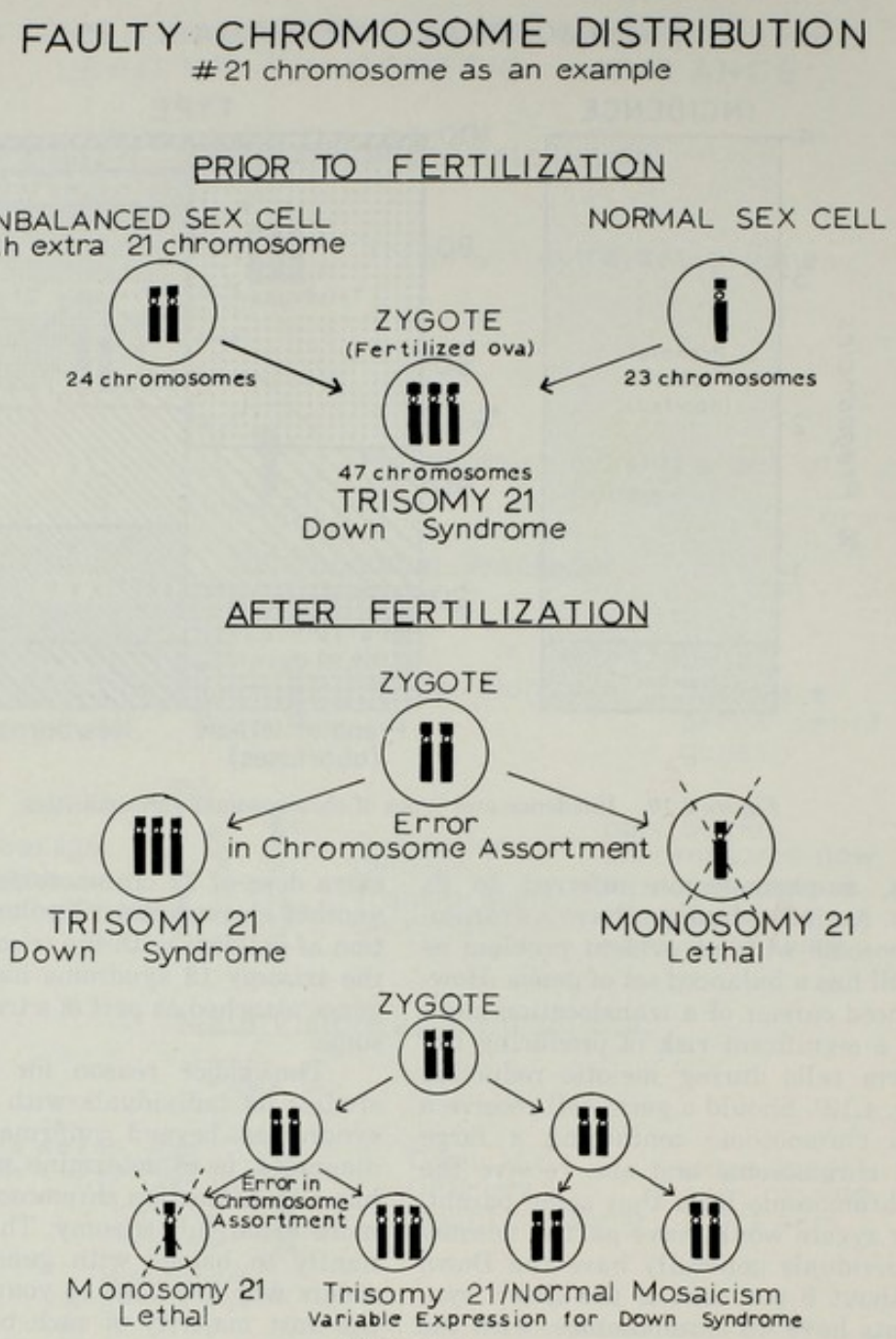


Figure 4.12.

cent) with a chromosomal abnormality, and these three died early in life. The utilization of the banding techniques for specific chromosome identification should allow for more accurate identification of such disorders, in terms of the piece which is missing or extra.

Another type of chromosomal abnormality which can lead to genetic imbalance is misdivision or breakage at the centromere during mitosis leading to the formation of an isochromosome, as depicted in Figure 4.9. The cell receiving the isochromosome has an extra dose of the long arm of the altered chromosome and is missing the set of genes on the short arm of that chromosome. Occasional cases of the autosomal trisomy syndromes may be found to have a presumed isochromosome of the long arm of 21, 13, or 18 chromosome causing the genetic imbalance. Also, X isochromosome-X has not been infrequent in individuals who have partial expression of the XO syndrome.

Counseling for Chromosomal Abnormalities

Autosomal Trisomy Syndromes

1. If there is any question as to assurance of the diagnosis, if the mother is young (generally less than 30 years), or if there are other cases of the same syndrome in the family pedigree, then chromosomal studies should be carried out on the patient in order to determine whether it is a full trisomy or a translocation case. If it is a full trisomy, then the future risk for younger mothers is less than 1 per cent, and for older mothers it is about the same as for any mother of

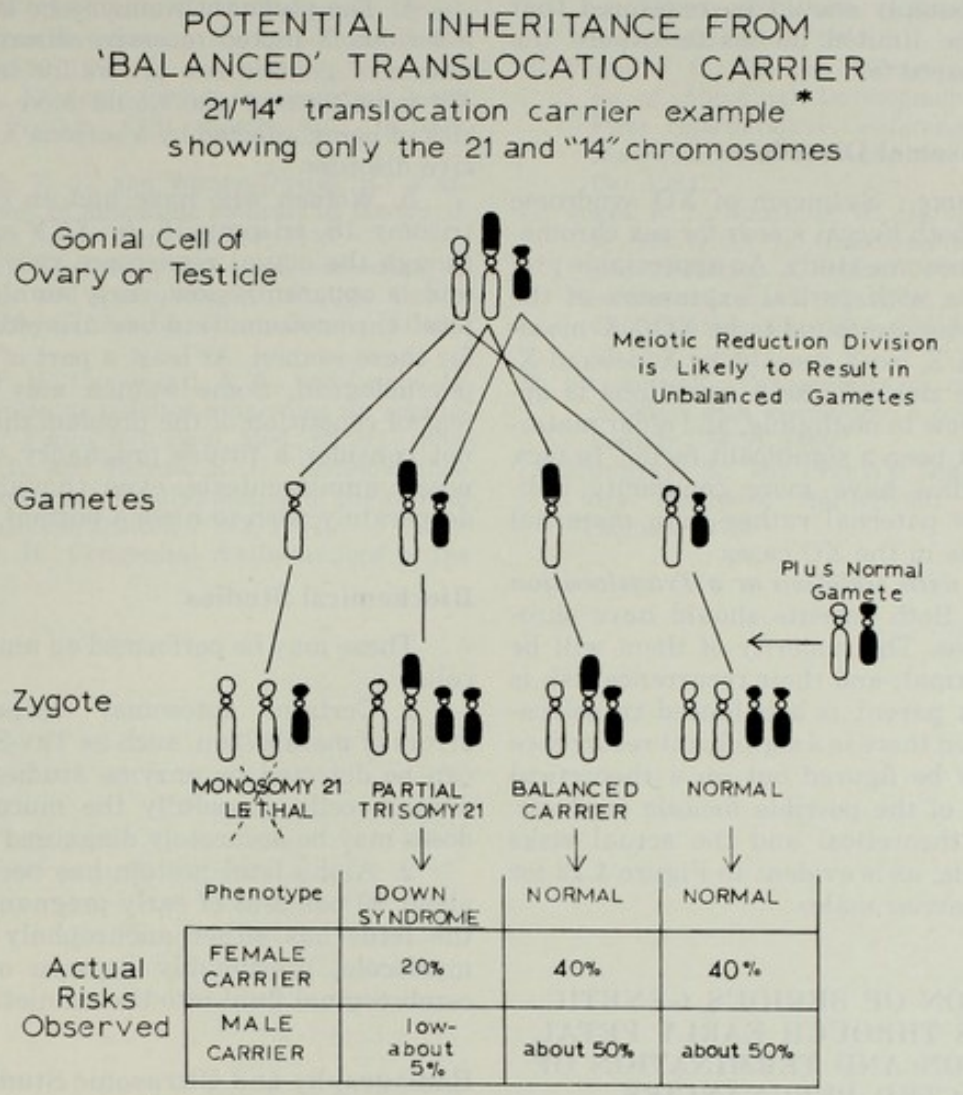


Figure 4.13.

that age (see Fig. 4.11). Should it be a translocation case, both parents should be studied to determine whether either parent is a balanced translocation carrier, a finding in about one third of such cases. The recurrence risk from chromosomally normal parents is apparently very small, certainly less than 1 per cent. The recurrence risk from a translocation carrier parent is obviously greater, but often less than the theoretical possibilities might indicate (see Fig. 4.12).

2. Inform the parents that the chromosome abnormality amounts to a gross genetic imbalance which upsets the pattern of development. Then explain what is *usual* for this genetic imbalance—the natural history for the syndrome.

3. For the trisomy 18 or 13 syndromes the parents may be told that most affected individuals with these trisomies are so seriously affected that they do not survive the first few months of pregnancy and that the parents "must have a good genetic background" and/or the mother "must be very good at carrying babies" in order for a baby with such a genetic imbalance to have survived to be born. Thus the parents may be helped to view the situation as a "late miscarriage." This sets the stage for informing them of the limited capacity for postnatal survival, the outcome if the baby should survive early infancy, and the indications for providing comfort without medical intervention towards survival, if they are in agreement with this approach. Whether the parents take the baby home or have the baby taken care of elsewhere is their

decision; they simply should be reassured that survival will be limited no matter where the baby is being cared for.

Other Chromosomal Disorders

XO Syndrome. Suspicion of XO syndrome should lead to both buccal smear for sex chromatin *and* a chromosome study. An appreciable proportion of cases with partial expression of the full XO syndrome are found to be XO/XX mosaic, X iso-X, XX/X iso-X mosaic, or X deleted-X. The recurrence risk for these conditions is apparently very low to negligible, and older maternal age has not been a significant factor. In fact, X-linkage studies have more commonly indicated a lack of paternal rather than maternal sex chromosome in the XO cases.

Any Case with Deletion or a Translocation Chromosome. Both parents should have chromosomal studies. The majority of them will be found to be normal, and their recurrence risk is negligible. If a parent is a balanced translocation carrier, then there is a significant recurrence risk. This may be figured out on a theoretical basis in terms of the possible meiotic products. However, the theoretical and the actual risks may not coincide, as is evident in Figure 4.13 for translocation carrier males.

PREVENTION OF SERIOUS GENETIC DISORDERS THROUGH EARLY FETAL RECOGNITION AND TERMINATION OF AFFECTED PREGNANCIES

It is becoming increasingly possible to evaluate the early developing fetus in an attempt to detect serious disorders early enough to allow for termination of affected pregnancies when there is a significant risk, often a recurrence risk, of a serious disorder.[13] The following are some of the techniques of early fetal evaluation and indications for their application, especially for single defects and patterns of malformation.

Chromosomal Abnormalities

Chromosome studies on the developing fetus can be done on cultured amnion cells at 13 to 15 gestational weeks and presently represent the most common indication for amniocentesis. Such studies should be considered for:

1. Older pregnant women. The overall incidence of aneuploidy climbs progressively after 35 years. Beyond 40 years the incidence of aneuploidy is about one in 40 pregnancies, the most common being trisomy 21.

2. Young pregnant women (under 30) who have had a trisomy 21 child. The recurrence risk is close to 1 per cent.

3. A potential parent who is a balanced translocation carrier and has a significant risk of having a genetically unbalanced offspring.

4. The pregnant woman who is a carrier for a serious X-linked recessive disorder. Determination of genetic sex allows for termination of XY male fetuses who would have a 50 per cent risk of being affected by a serious X-linked recessive disorder.

5. Women who have had an offspring with trisomy 18, trisomy 13, or XXY syndrome. Although the actual recurrence risk is not known and is apparently low, early amniocentesis and fetal chromosomal studies are often considered for these women. At least a part of the reason is psychological. Some women may have such a fear of repetition of the problem that they would not consider a future pregnancy without diagnostic amniocentesis, even though they might desperately wish to have a normal child.

Biochemical Studies

These may be performed on amniotic fluid or cells.

1. Certain autosomal recessive inborn errors of metabolism, such as Tay-Sachs disease, can be detected by enzyme studies on cultured amnion cells. Hopefully the mucopolysaccharidoses may be accurately diagnosed in utero also.

2. Alpha fetal protein has been detected in about 90 per cent of early pregnancies in which the fetus has either anencephaly or meningomyelocele, presumably because of leakage of cerebrospinal fluid into the amniotic space.

Radiography and Ultrasonic Studies

1. The dimensions of the fetal head can be outlined and measured by sonography by 14 to 16 weeks of fetal life, allowing for early termination of affected fetuses with primary microcephaly (often autosomal recessive) and anencephaly.

2. Roentgenographic studies of the fetal skeleton may allow for early detection of an affected fetus with a gross skeletal defect. One example is the radial aplasia-thrombocytopenia syndrome, an autosomal recessive disorder. The radius is ossified by 16 weeks and visualization of the ulna with no radius by 16 weeks could be used as evidence to detect a recurrence of this disorder.

Direct Fetoscopy

Fiberoptic fetoscopes are now being developed with the hope that they may provide direct visualization of the fetus for evidence of external malformation and also permit fetal blood samples to be obtained.

REFERENCES

1. Carter, C. O.: The inheritance of common congenital malformations. Progr. Med. Genet., *4*:59, 1965.

2. Smith, D. W., and Aase, J. M.: Polygenic inheritance of certain common malformations. J. Pediatr., *76*:653, 1970.
3. Nora, J. J.: Etiologic factors in congenital heart disease. Pediatr. Clin. North Am., *18*:1059, 1971.
4. Riseborough, E. J., and Wynne-Davies, R.: A genetic survey of idiopathic scoliosis in Boston. J. Bone Joint Surg. [Am.], *55*:974, 1973.
5. Ching, G. H. S., Chung, C. S., and Nemechek, R. S.: Genetic and epidemiological studies of clubfoot in Hawaii. Am. J. Hum. Genet., *21*:566, 1969.
6. Saldanha, P. H., Cavalcanti, A. A., and Lemos, M. S.: Incidencia de defeitos congenitos na populacao de Sao Paulo. Rev. Paul. Med., *63*:211, 1963.
7. McKeown, T., and Record, R. G.: Seasonal incidence of congenital malformation of the central nervous system. Lancet, *1*:192, 1951.
8. Edwards, J. H.: Congenital malformations of the central nervous system in Scotland. Br. J. Prev. Soc. Med., *12*:115, 1958.
9. Fraser, F. C.: The Use of Teratogens in the Analysis of Abnormal Developmental Mechanisms. First International Conference on Congenital Malformations. Philadelphia, J. B. Lippincott Co., 1961.
10. Jones, K. L., Smith, D. W., Harvey, M. A., Hall, B. D., and Quan, L.: Older paternal age and fresh gene mutation. J. Pediatr., *86*:84, 1975.
11. Herrmann, J.: Ein Einfluss des zeugungsalters auf die Mutationen zu Hämophilie A. Humangenetik, *3*:1, 1966.
12. Summitt, R.: Cytogenetics in mentally retarded children with anomalies: A controlled study. J. Pediatr., *74*:58, 1969.
13. Milunsky, A.: The Prenatal Diagnosis of Hereditary Disorders. Springfield, Ill., Charles C Thomas, 1973.

Chapter Five

THE PSYCHOLOGICAL ADAPTATION

to the child with a malformation problem

During pregnancy the prospective parents anticipate a normal child, but many have a lingering fear that the baby may be abnormal. When told that the baby does have a malformation problem, their initial response is often denial, mixed with such feelings as guilt, anxiety, self-pity, and sadness. The latter emotion may partially represent a grief response to the "loss" of the anticipated normal child. The situation can present a smashing blow to the ego of one or both parents and may become a major threat to their marriage. The knowledge and counseling approach of the physician can play an integral role in the realistic adaptation of the parents to this unexpected problem. The physician's knowledge is important in arriving at a correct diagnosis, prognosis, management plan, and genetic counsel. Ideally, the approach involves informing *both* parents of the facts and indicating probable consequences of the situation for the baby and the family. Once the parents have been given an honest perspective of the problem, it is important to involve them integrally in any decisions which need to be made. In fact, given adequate knowledge and counsel, it is the parents who should make the paramount decisions. Depending on the nature of the disorder and the desires of the parents, management may vary from no medical intervention with the anticipation of limited survival at one extreme, to full intervention in terms of survival and functional adaptation at the other.

One Extreme: Option of No Medical Intervention

The author's approach includes giving the parents the option of no medical intervention for disorders in which there is a severe defect in brain development and function and also for those problems which will severely limit the capacity of the baby to survive and function, even with full medical intervention. Examples include anencephaly and some of the other more severe neural tube defects, hydranencephaly, holoprosencephaly, the trisomy 18 syndrome, the trisomy 13 syndrome, the 4p− syndrome, and the Meckel-Gruber syndrome. The parental counseling approach is set forth for two of these disorders:

1. Anencephaly, as an isolated defect: The parents are informed about the neural groove and how it usually closes by 28 days of development to form the neural tube, the forerunner of the brain. Failure of this neural groove closure has resulted in the severe problem in early brain morphogenesis for their baby. They are then told that about 1 per cent of developing fetuses have such a neural tube defect, of which 90 per cent do not survive to be born and are spontaneously aborted. The mother can be told: "You must be well suited for carrying children to have carried a baby with this problem to full term. Having survived intrauterine life, its capacity for continued survival is limited. If we intervene to maintain survival, the baby's function will be severely limited. We feel that the kindest approach is that of no medical intervention. Do we have your permission for such an approach?" The anomaly is thus explained from a developmental viewpoint, the situation is interpreted as a late miscarriage, and the parents are given the option of no medical intervention.

2. The trisomy 18 or trisomy 13 syndromes: The parents are told that normal development is dependent on a balanced set of genes and that

the baby has a genetic imbalance due to an extra 18 or 13 chromosome. They are then told, "At least 4 per cent of recognized pregnancies begin with such an extra chromosome. Most of those with an extra 18 or 13 chromosome do not survive early fetal life and are miscarried. You must be very well suited for carrying babies to have had a baby with this extra chromosome who survived to be born. Although the baby survived intrauterine life, its capacity to survive outside of you is limited. If we intervene and try to prolong life, the baby's function will be extremely limited. We feel the kindest approach is to let nature take its course by not intervening from the medical standpoint. Do we have your permission for this approach?" Thus, the parents are told the basic cause of the problem, helped to interpret the situation as a late miscarriage, and given the option of no medical intervention.

The Other Extreme: Interpretation as a "Normal Child"

At the other extreme are those babies with a malformation disorder which can be adequately managed so that it need not impair the child's capacity to lead a normal life. Included are otherwise normal infants with a single defect such as cleft lip, pyloric stenosis, polydactyly, most instances of dislocation of the hip and club foot, some instances of cardiac anomalies, etc. The following is the author's approach in counseling parents about such defects, using isolated cleft lip as an example. "Your *baby* is normal. There was a problem in the full closure of the lip. This is a normal stage in development of the lip, which usually closes by 35 days in utero. A plastic surgeon can bring about complete closure and the result is usually quite acceptable. The reason I stated that your *baby* is normal is that I do not believe that this problem in closure of the *lip* need interfere with your child's leading a normal life." Thus the anomaly is explained from a developmental viewpoint, its management is discussed, and its impact on the child is explained. A major emphasis is placed on stating that the baby is normal and localizing the problem in realistic terms of what it represents—a correctable anomaly which need not handicap the child. Hopefully, such counsel will be of value in bringing about a realistic acceptance of the baby by the parents. Hence, *acceptance* of the whole child becomes the key to the approach. Until there is acceptance, the normal flow of affection between parents and child may be warped in the unfortunate directions of either rejection or overprotection.

The Intermediate Situation: The Chronically Handicapped Child

There are a number of malformation disorders which fall in between the previously mentioned extremes with regard to counseling. The approach for these conditions is usually an individualized one, depending on the nature and severity of handicap engendered by the disorder. The parents should be given facts relative to the cause of the problem, the *usual* range of functional limitations for the disorder, and what can be done to help the child adapt. For these conditions the approach is to help the parents accept the child *with his problem.* It is often worthwhile to have the family meet with other families or groups of individuals who have the same type of problem. For example, the Little People of America can help individuals with shortness of stature, and the National Association for Retarded Children may be supportive to a family which has a child with mental deficiency.

The physician who provides counsel for problems of malformation should be prepared to devote considerable time to the effort. The parents may comprehend and retain only part of the initial counsel, at least partly because of the emotional shock of the situation. The physician should also realize that there may be initial resentment toward the counselor because the information he is presenting has not yet been accepted by the parents. Finally, it is important to appreciate that there is great variability in the acceptance of a child with a malformation problem. Some individuals seem almost incapable of accepting a handicapping disorder; others can develop a genuine bond of deep parental love for a handicapped child.

REFERENCE

1. Miller, L. G.: Toward a greater understanding of the parents of the mentally retarded child. J. Pediatr., *73*:699, 1968.

Chapter Six

MINOR MALFORMATIONS

as clues to more serious problems and toward the recognition of malformation syndromes

Minor anomalies are herein defined as unusual morphologic features that are of no serious medical or cosmetic consequence to the patient. The value of their recognition is that they may serve as indicators of altered morphogenesis in a general sense or may constitute valuable clues in the diagnosis of a specific pattern of malformations.

Regarding the general occurrence of minor anomalies detectable by surface examination (except for dermatoglyphics), Marden, Smith, and McDonald[1] found that 14 per cent of newborn babies had a single minor anomaly. This was of little concern because the frequency of major defects in this group was not appreciably increased. However, only 0.8 per cent of the babies had two minor defects, and in this subgroup the frequency of a major defect was five times that of the general group. Of special importance were the findings in babies with three or more minor anomalies. This was found in only 0.5 per cent of babies (20), and 90 per cent of them had one or more major defects as well, as depicted in Figure 6.1. In summary, the finding of several minor anomalies in the same individual is unusual and often indicates that a more serious problem in morphogenesis has occurred.

These minor external malformations are most common in areas of complex and variable features such as the face, auricles, hands, and feet. Before ascribing significance to a given minor anomaly in a patient it is well to note whether it is found in other family members. Almost any minor defect may occasionally be found as a usual feature in a particular family, as noted in Figure 6.2.

The following figures illustrate certain minor anomalies and allude to their developmental origin and relevance. Also depicted, for

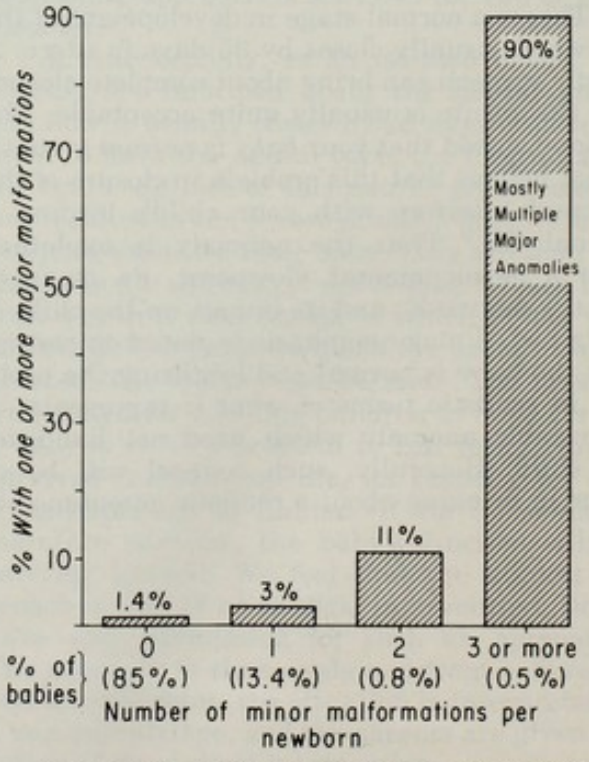


Figure 6.1. Frequency of major malformations in relation to the number of minor anomalies detected in a given newborn baby. (From Marden, P. M., Smith, D. W., and McDonald, M. J.: J. Pediatr., *64*:357, 1964.)

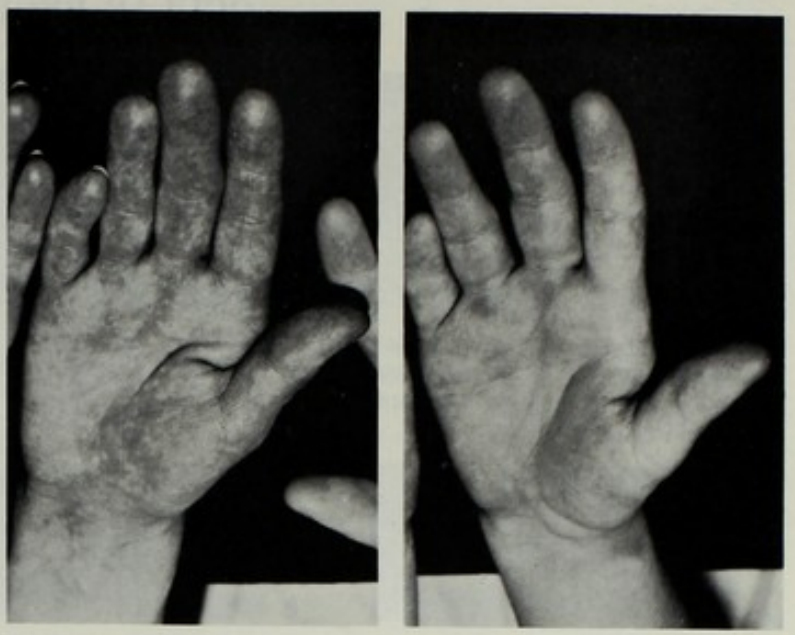


Figure 6.2. An otherwise normal mother (*left*) and daughter with clinodactyly of the fifth finger. A family history should be obtained before ascribing significance to a given minor anomaly.

perspective, are some minor variants found in the newborn babies with sufficient frequency that they should not be classed as anomalies.

CALVARIUM

The presence of unusually *large fontanels* (see standards in Chapter Seven) may be a nonspecific indicator of a general lag in osseous maturation. It may, for example, lead to the detection of congenital hypothyroidism in the newborn or in early infancy, as shown in Figure 6.3. The finding of a large posterior fontanel is especially helpful in this regard, since the posterior fontanel is normally fingertip size or smaller in 97 per cent of full-term newborns. Large fontanels may also be a feature in certain skeletal dysplasias and can, of course, be a sign of increased intracranial pressure.

(*Text continued on page 439*)

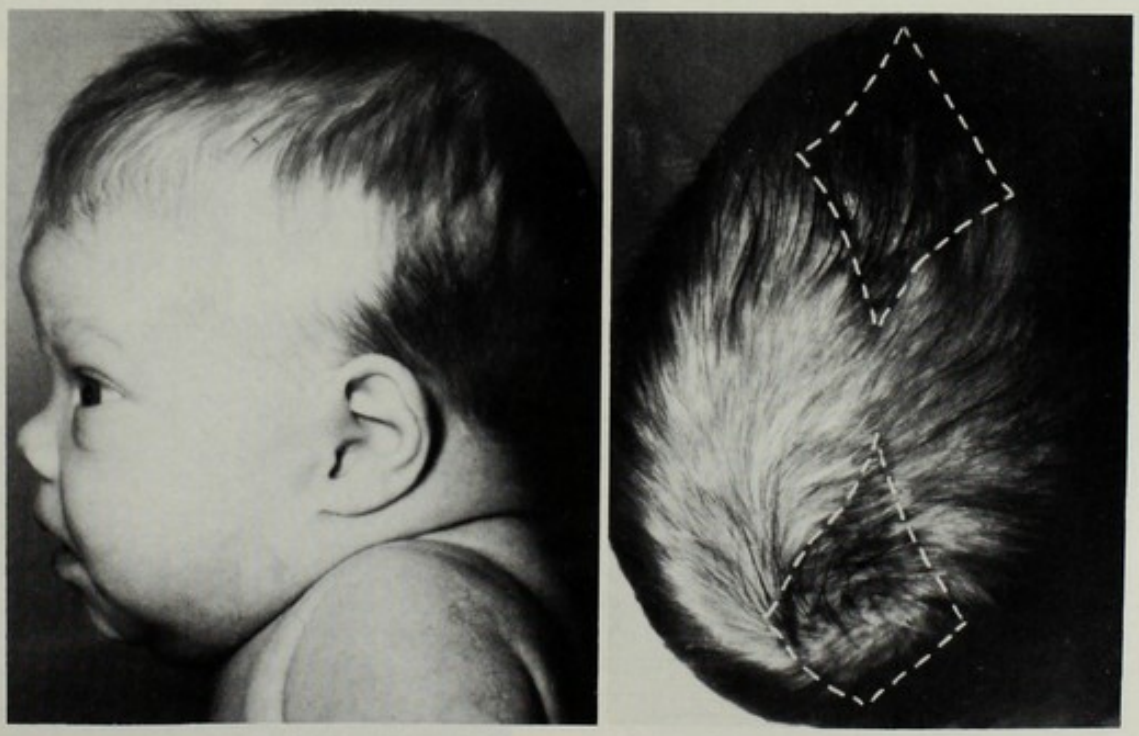
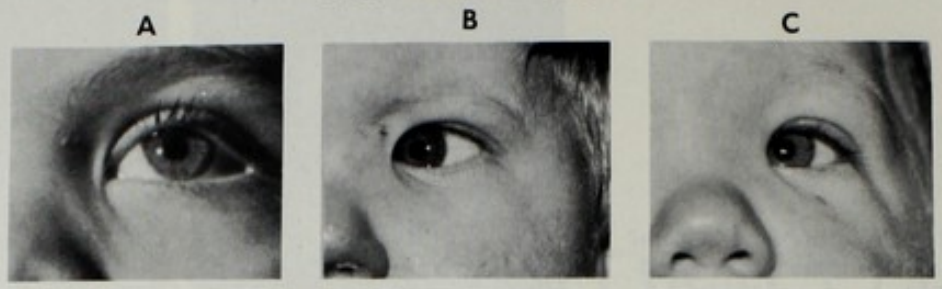


Figure 6.3. Unusually large fontanels, especially the posterior fontanel, in a six week old baby with athyrotic hypothyroidism. The fetal onset of retarded osseous maturation is also evident in the immature facial bone development. (From Smith, D. W., and Popich, G.: J. Pediatr., *80*:753, 1972.)

OCULAR REGION



A–C, Inner epicanthal folds appear to represent redundant folds of skin, secondary to either low nasal bridge (most common) or excess skin, as in cutis laxa. Minor folds are frequent in early infancy, and as the nasal bridge becomes more prominent they are obliterated.



A and B, Telecanthus is the consequence of lateral displacement of the inner canthi, which partially obscures the medial portion of the eye and gives a false impression of strabismus.

C, Ocular hypertelorism indicates widely spaced eyes. Low nasal bridge will often give rise to a visual impression of ocular hypertelorism. This should always be determined by measurement. Measurement of inner canthal distance, coupled with the visual distinction of whether telecanthus is present or not, is usually sufficient.

A and C, Slanting of the palpebral fissures. The alignment of the palpebral fissures seems to be secondary to the early growth rate of the brain above the eye versus that of the facial area below the eye. For example, the patient with upslanting (*A*) had mild microcephaly with a narrow frontal area, resulting in the upslant; the patient with downslanting (*B*) had maxillary hypoplasia, resulting in the downslant.

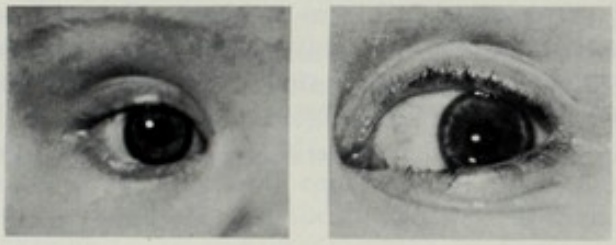


Figure 6.4. Brushfield spots: speckled ring about 2/3 of distance to periphery of iris with relative lack of patterning beyond it. Found in about 20% of individuals vs. 80%, and more striking in the Down syndrome.

ORAL REGION

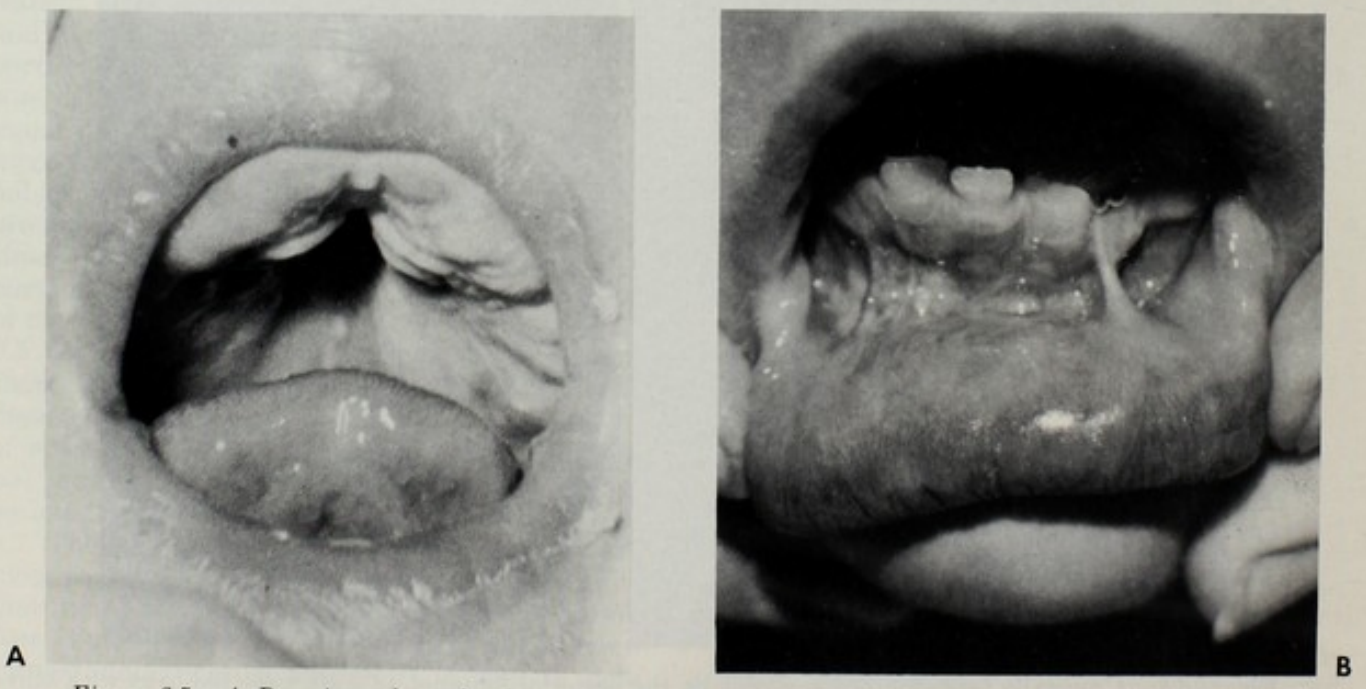
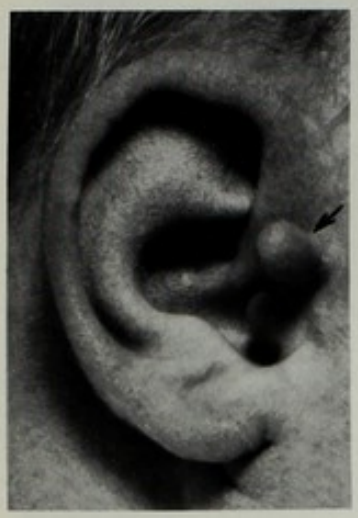
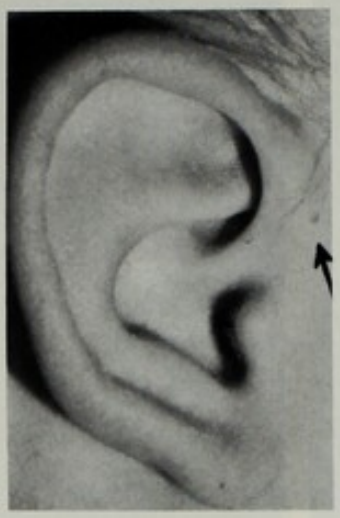


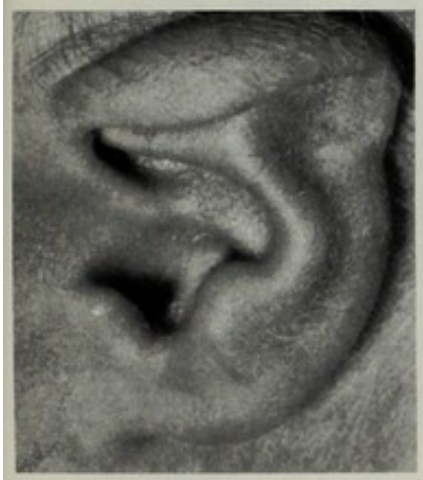
Figure 6.5. A, Prominent lateral palatal ridges. This may be secondary to a deficit of tongue thrust into the hard palate, allowing for relative overgrowth of the lateral palatal ridges. It may be a feature in a variety of disorders, especially those with hypotonia and those with serious neurologic deficits relative to sucking. As such it can be a useful sign of a long-term deficit in function. *B, Aberrant frenula.*

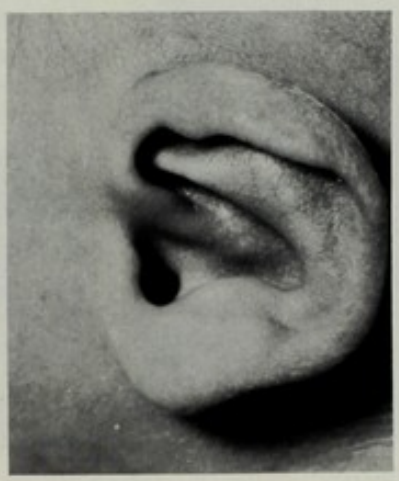
AURICULAR REGION





Preauricular tags, which often contain a core of cartilage, appear to represent accessory hillocks of His, the hillocks which normally develop in the recess of the mandibular and hyoid arches and coalesce to form the auricle. *Preauricular pits* may be familial, are twice as common in females as in males, and are more common in blacks than in whites.





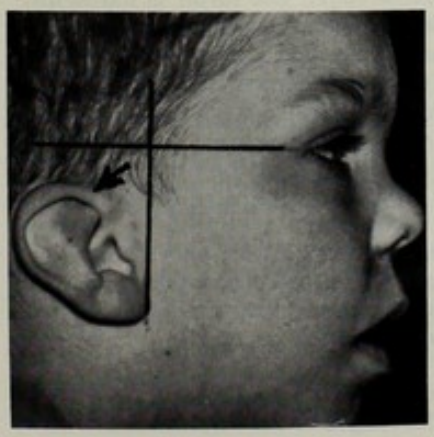
Incomplete scapha helix development (minor degrees not unusual in infants).



Lack of lobulus



Prominent ear

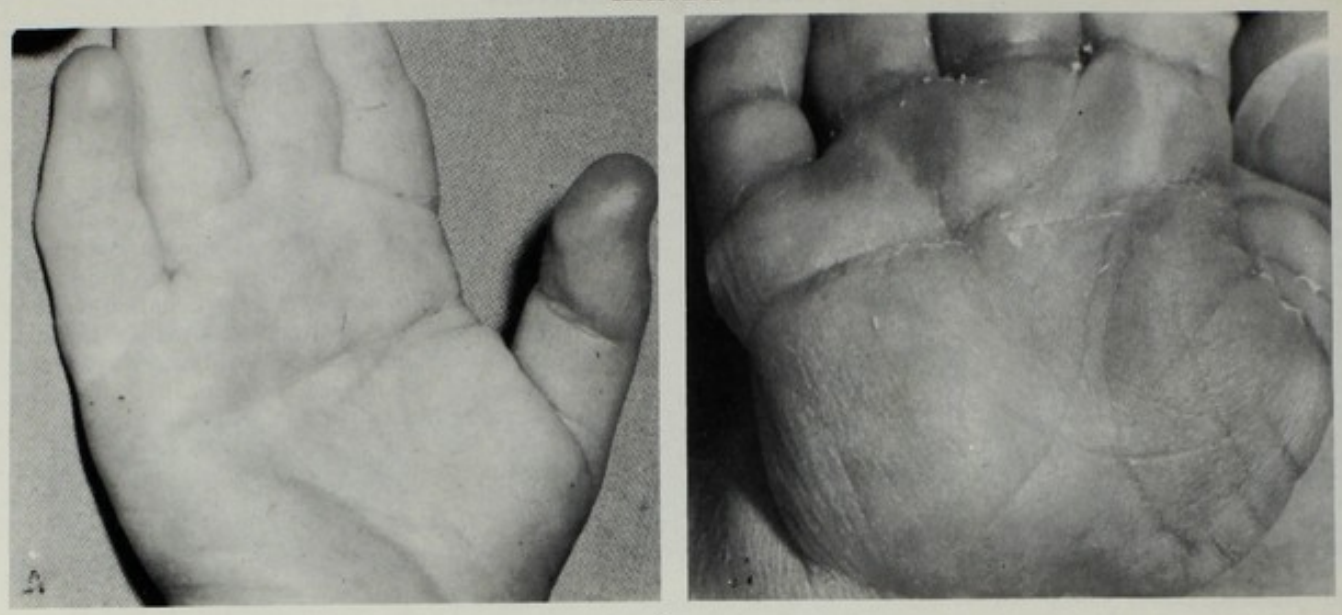


Ears low-set: This designation is made when the helix meets the cranium (*arrow*) at a level below that of a horizontal plane with the corner of the orbit. This latter plane may relate to the lateral vertical axis of the head. More ideally, the horizontal plane may be an extension of a line through both inner canthi, such as can be done with a pliable strip of x-ray film.

Ears slanted: When the angle of the slope of the auricle exceeds 10 degrees from the perpendicular. Note: The findings of low placement and slanted auricle often go together and usually represent a lag in morphogenesis, since the auricle is normally in that position in early fetal life.

Figure 6.6.

HANDS



A



B

Figure 6.7. *A, Creases* represent the planes of folding (flexion) of the thickened volar skin of the hand. As such they are simply deep wrinkles. The finger creases relate to flexion at the phalangeal joints, and if there has been no flexion there is no crease. Hypoplasia of the middle phalanx may result in only one plane of flexion on that finger *(left).* The hypothenar crease is the consequence of oppositional flexion of the thumb. Hence, if there is no oppositional flexion there will be no crease. The slanting upper palmar crease reflects the palmar plane of folding related to the slope of the third, fourth, and fifth metacarpal-phalangeal joints. The midpalmar crease is the plane of skin folding between the upper palmar crease and the hypothenar crease. Any alteration in the slope of the third, fourth, and fifth metacarpal-phalangeal plane of flexion, or relative shortness of the palm, may give rise to but a single midpalmar plane of flexion and thereby the *simian crease (left).* The latter is found unilaterally in about 4 per cent of normal infants and bilaterally in 1 per cent. Davies[4] found the incidence to be 3.7 per cent in newborn babies and noted that the simian crease is twice as common in males as in females. All degrees are found between normal and *simian crease,* including the *bridged palmar crease (right).*

The creases are evident by 11 to 12 weeks of fetal life; hence, any gross alteration in crease patterning is usually indicative of an *abnormality in form and/or function of the hand prior to 11 fetal weeks.*[5]

B, The *nails* generally reflect the size and shape of the underlying distal phalanx. Hence, the *short broad nail (left),* the *narrow hyperconvex nail (middle),* and the *hypoplastic nail (right)* reflect the relative dimensions of the underlying respective phalanges.

Asymmetric length (B, right) of fingers is usually the result of hypoplasia of one or more fingers.

Clinodactyly (curved finger) (see *A, left)* is most common in the fifth finger and is the consequence of hypoplasia of the middle phalanx, normally the last digital bone to develop. Up to 8 degrees of inturning of the fifth finger is within normal limits. Regardless of which digit is affected (fingers or toes), there is usually incurvature toward the area between the second and third digits.

Camptodactyly (bent finger, B, right) most commonly affects the fifth, fourth, and third digits in decreasing order of frequency. It is presumably the consequence of relative shortness in the length of the flexor tendons with respect to the growth of the hand.

Partial *cutaneous syndactyly* (see *A, left)* represents an incomplete separation of the fingers and most commonly occurs between the third and fourth fingers and between the second and third toes.

DERMAL RIDGE PATTERNS

(DERMATOGLYPHICS)

The parallel dermal ridges on the palms and soles form between the thirteenth and nineteenth fetal weeks. Their patterning appears to be dependent on the surface contours at that time, and the parallel dermal ridges tend to develop transversely to the planes of growth stress.[6] Curvilinear arrangements occur where there was a surface mound, as over the fetal pads which are prominently present during early fetal life on the fingertips, on the palm between each pair of fingers, and occasionally in the hypothenar area. Indirect evidence suggests that a high fetal fingertip pad tends to give rise to a whorl pattern, a low pad yields an arch pattern, and an intermediate pad produces a loop, as illustrated in Figure 6.8*B*.

The dermal ridge patterning thereby provides an indelible historical record that indicates the form of the early fetal hand (or foot). Mild to severe alterations in hand morphology occur in a variety of syndromes, and hence it is not surprising that dermatoglyphic alterations have been noted in numerous dysmorphic syndromes. These alterations have seldom been pathognomonic for a particular condition. Rather, they simply provide additional data which, viewed in relation to the total pattern of malformation, may enhance the clinician's capacity to arrive at a specific overall diagnosis.

Dermal ridge patterning may be evaluated utilizing a seven-power illuminated magnifying device such as an otoscope or a stamp-collector's flashlight which has a wider field of vision. Permanent records may be obtained by a variety of techniques.[7-9]

There are two general categories of dermatoglyphic alterations: an *aberrant pattern* and an *unusual frequency* and/or *distribution of a particular pattern on the fingertips.*

Aberrant Patterning

Distal Axial Palmar Triradius (Fig. 6.8A). Triradii occur at the juncture of three sets of converging ridges. There are usually no triradii between the base of the palm and the interdigital areas of the upper palm. However, patterning in the hypothenar area often gives rise to a distal axial triradius located, by definition, greater than 35 per cent of the distance from the wrist crease to the crease at the base of the third finger. This alteration, found in about 4 per cent of Caucasians, is a frequent feature in a number of patterns of malformation.

Open Field in Hallucal Area (Arch Tibial) (Fig. 6.8*A*). Open field simply means a relative lack of complexity in patterning and thereby implies a low surface contour in that area at the time ridges developed. The hallucal area of the sole usually has a loop or whorl pattern and a lack of such pattern is unusual in the normal but is found in about 50 per cent of patients with the Down syndrome and as an occasional feature in other syndromes.

Lack of Ridges. Failure of development of ridges in an area, most commonly the hypothenar area of the palm, is an occasional but nonspecific feature in the de Lange syndrome.

Other Patterns. There are a number of other unusual patterns, especially in the upper palmar, hypothenar, and thenar areas, which may be of clinical significance, but these are so rarely of value in an individual case that they will not be discussed.

Unusual Frequency or Distribution of Patterns on the Fingertips

A quantitation of the overall extent of patterning on the ten fingertips may be achieved by obtaining fingerprints and recording the total fingertip ridge count, as illustrated in Figure 6.8*C*.

High Frequency of Low Arch Configurations. It is unusual to find a normal person with more than six of ten fingertips having a low arch configuration; however, this is a frequent feature in the trisomy 18 syndrome and the XXXXY syndrome, presumably reflecting hypoplasia of the fetal fingertip pads in these disorders. High frequency of low arches is nonspecific, being an occasional finding in certain other syndromes and in about 0.9 per cent of normal individuals.

High Frequency of Whorl Patterning. It is unusual to find nine or more fingertip whorls in an individual (3 per cent in normals). Excessive patterning, presumably reflecting prominent fetal pads, is more likely to be found in the XO syndrome, the Smith-Lemli-Opitz syndrome, occasionally in other patterns of malformation, and in some normal individuals.

Unusual Distribution, Especially of Radial Loop Patterns. Loops opening to the radial side of the hand are unusual on the fourth and fifth fingers. Radial loop pattern on these fingers is more common in the Down syndrome (12.4 per cent) than in the normal (1.5 per cent).

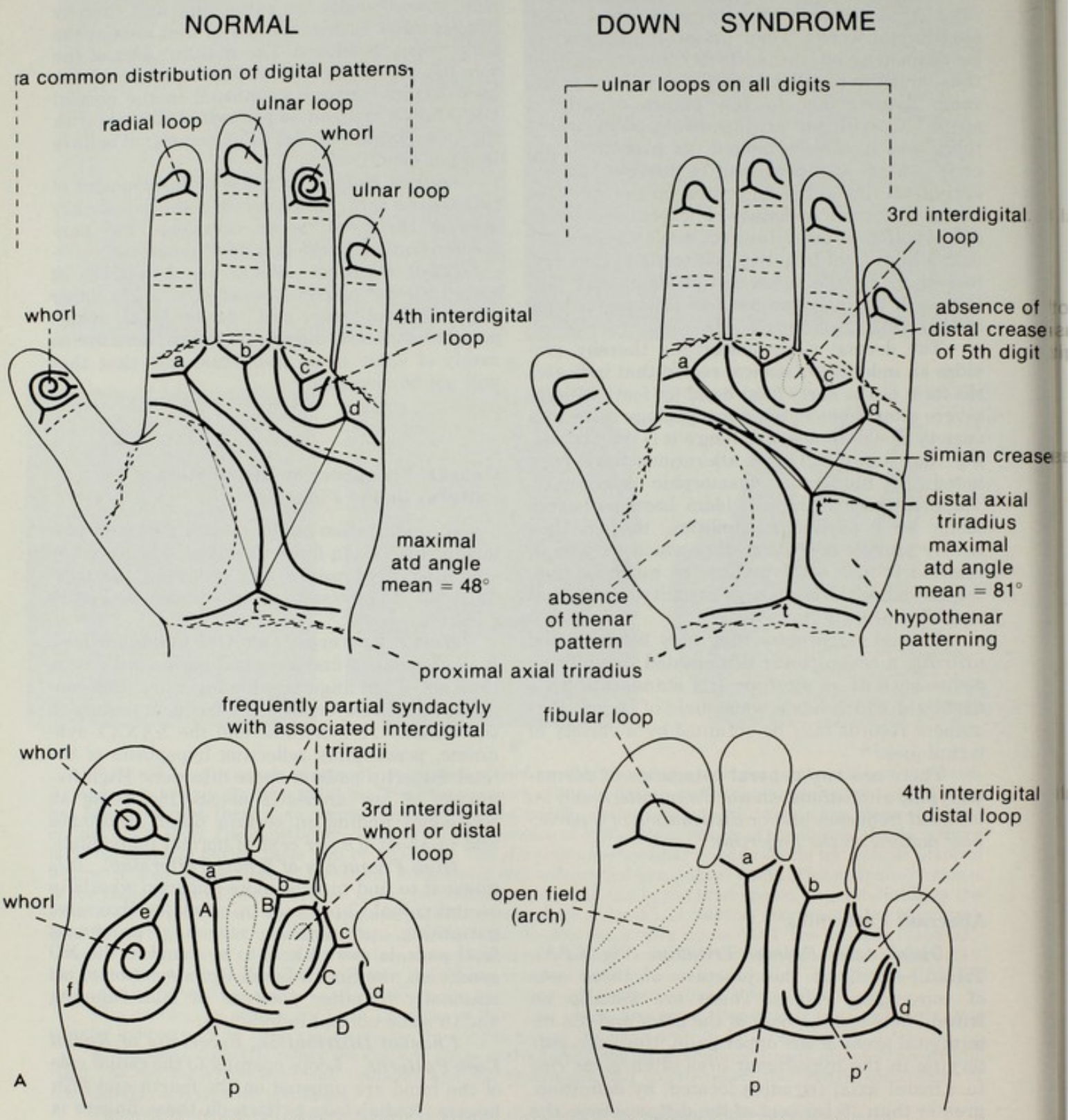


Figure 6.8. *A,* The solid lines and dotted lines denote the dermal ridge configurations, and the dashes within the palm represent the creases. (Courtesy of Dr. M. Bat-Miriam; prepared by Mr. R. Lee of the Kennedy-Galton Center near St. Albans, England.)

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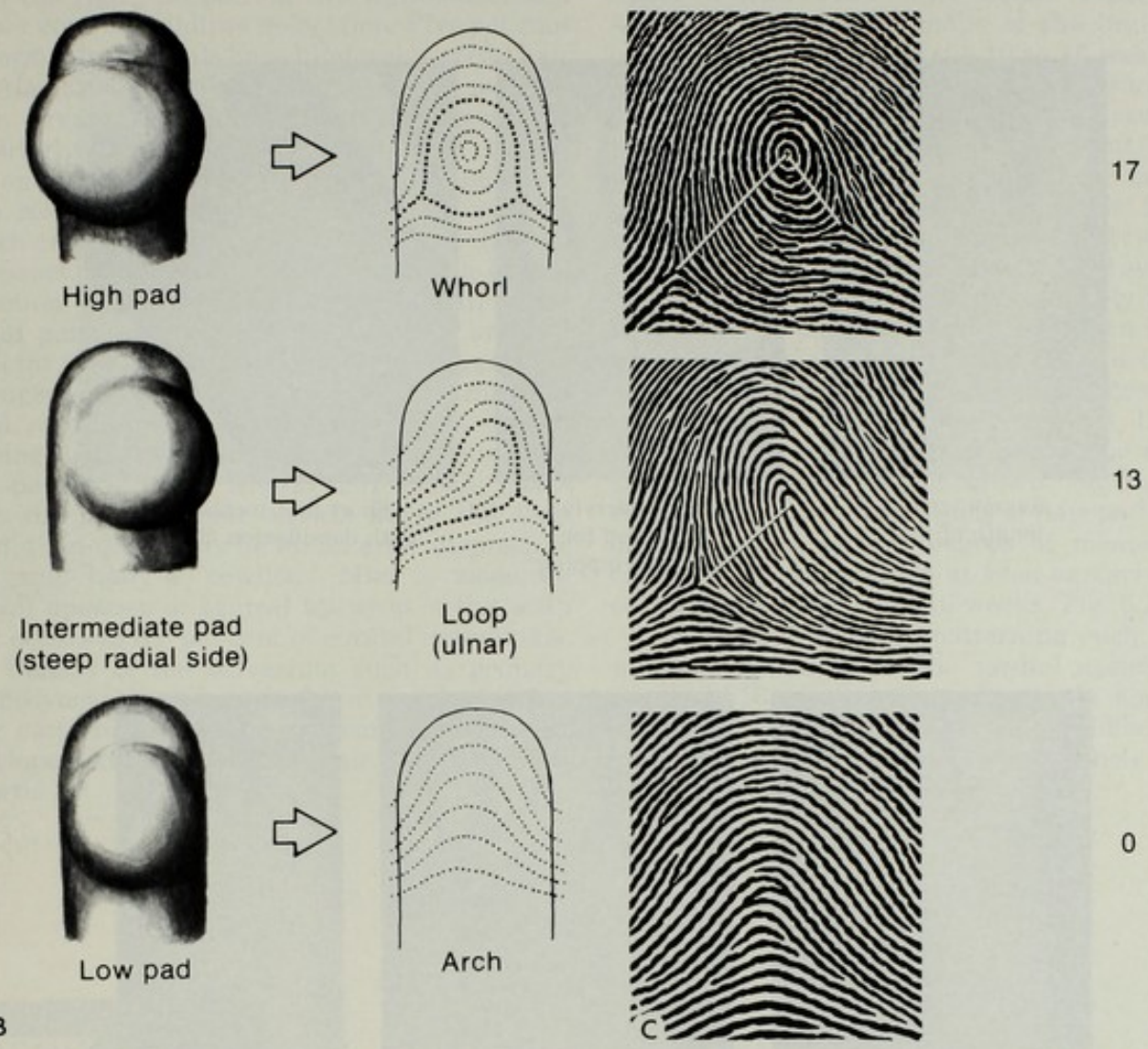


Figure 6.8 (Continued). *B*, Presumed relationship between fetal fingertip pads at 16 to 19 weeks of fetal life and the fingertip dermal ridge pattern, which develops at that time. *C*, Technique for dermal ridge counting: A line is drawn between the center of the pattern and the more distal triradius, and the number of ridges which touch this line is the fingertip ridge count. The sum of the ten fingertip ridge counts is the total ridge count; this averages 144 in the male and 127 in the female. (From Holt, S.: Br. Med. Bull., *17*:247, 1961.)

HAIR; ORIGIN AND RELEVANCE OF ABERRANT SCALP AND UPPER FACIAL HAIR PATTERNING AND GROWTH

The origin and relevance of hair directional patterning and of aberrant hair growth[10, 11] will be individually considered.

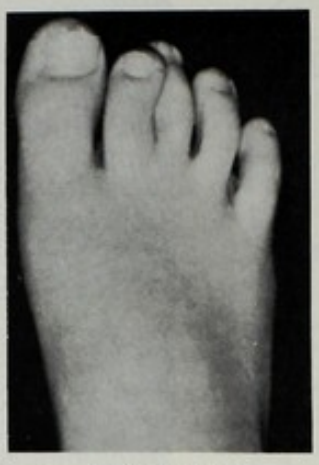
Hair Directional Patterning

Normal Development and Relevance. The origin of the sloping angulation of each hair follicle, which determines the surface hair directional patterning, is set forth by the direction of stretch on the surface skin during the time the hair follicle is growing down from it, into the loose underlying mesenchyme as shown in Figure 6.10. Over the scalp and upper face this directional patterning reflects the plane of growth stretch on the surface skin which was exerted by the growth of underlying structures during the period of hair follicle downgrowth, from 10 to 16 weeks of fetal life. Thus the parietal hair whorl, or crown, is interpreted as representing the focal point from which the posterior scalp skin was under growth tension exerted by the dome-like outgrowth of the early brain during this fetal period (see Fig. 6.11). Its location is normally several centimeters anterior to the position of the posterior fontanel. Fifty-six per cent of single parietal hair whorls are located to the left of the midline, presumably because the

FEET



Asymmetrical length of toes



Clinodactyly of second toe with overlapping



Short first metatarsal with dorsiflexion of hallux



Syndactyly, most common 2-3



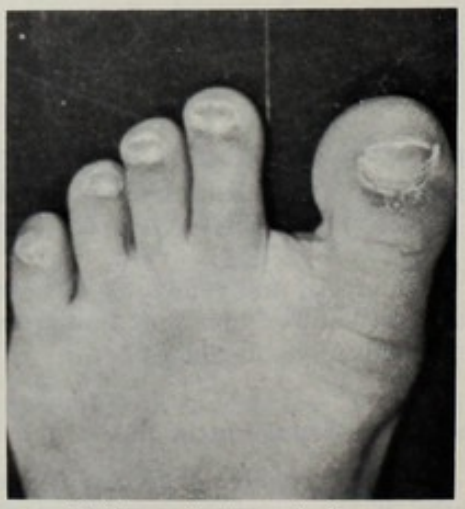
Hypoplasia of nails (2½ year old)



Short, broad toenail



Deep crease between hallux and second toe



Wide gap between hallux and second toe

Figure 6.9.

left side of the brain tends to be slightly larger than the right; 30 percent are right-sided, and 14 per cent are midline in location. Five per cent of normal individuals have bilateral parietal hair whorls. From the posterior whorl the parietal hair stream progressively outflares, sweeping anteriorly to the forehead. Over the frontal region the growth of the forebrain and the upper face results in bilateral frontal hair streams which emanate from the fixed points of the ocular puncta and tend to arc outward in a lateral direction, thereby affecting eyebrow hair directional patterning (see Fig. 6.12). The anterior parietal hair stream normally converges with the upsweeping frontal hair stream on the forehead, resulting in a variety of forehead hair patterning such as converging whorls and quadriradial patterns. If the frontal hair stream meets with the parietal hair stream above the forehead, then there may be an anterior upsweep of the scalp hair, a "cowlick." Mild to moderate lateral upsweep or central upsweep of the scalp hair occurs in 3.5 per cent of normal individuals.

Defects of the calvarium such as primary craniosynostosis have not been noted to affect hair patterning, since the calvarium is not yet developed at the time of hair follicle downgrowth.

Relevance and Nature of Aberrant Scalp and Upper Facial Hair Directional Patterning. Abnormal size and/or shape of the brain and upper facial area during the 10 to 16 week fetal period can apparently result in aberrant hair patterning. Severe microcephaly may result in a lack of a parietal hair whorl (25 per cent) and/or a frontal upsweep of the scalp hair (70 percent) as shown in Figure 6.13. The latter feature appears to relate to a narrow and smaller frontal area of the brain. The parietal whorl is more likely to be midline and posteriorly located in patients with microcephaly, as shown in Figure 6.14. In a variety of other gross defects of early brain development the hair directional patterning may be secondarily altered. In each case the aberrant scalp hair patterning reflects the altered shape and/or growth of the early fetal brain. Gross aberrations of hair patterning often imply a serious degree of mental deficiency, since the brain is at such an early stage of development at 10 to 16 weeks (Fig. 6.15).

Abnormal eyebrow patterning such as the unusual outflaring of the medial eyebrows in Figure 6.16 implies that there was abnormal shape and/or growth in the upper midface prior to or during the period of hair follicle downgrowth, from 10 to 16 weeks.

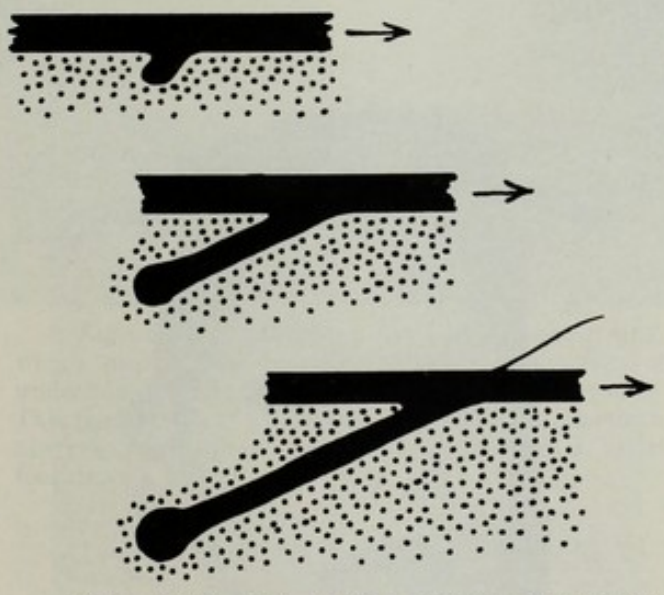


Figure 6.10. Hair follicles over the scalp begin their downgrowth into the loose underlying mesenchyme at ten fetal weeks. The slope of each hair follicle and thereby the hair directional patterning is determined by the direction of growth stretch *(arrows)* exerted on the surface skin by the development of underlying tissues. For the scalp hair, the patterning relates to the growth in size and form of the underlying brain during the period of 10 to 16 weeks. By 18 weeks, when hairs are extruded onto the surface, their patterning is set. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)



Figure 6.11. Parietal hair whorl at 18 weeks. This appears to be the focal fixed point from which the skin is under stretch by the dome-like outgrowth of the brain between 10 and 16 weeks. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)

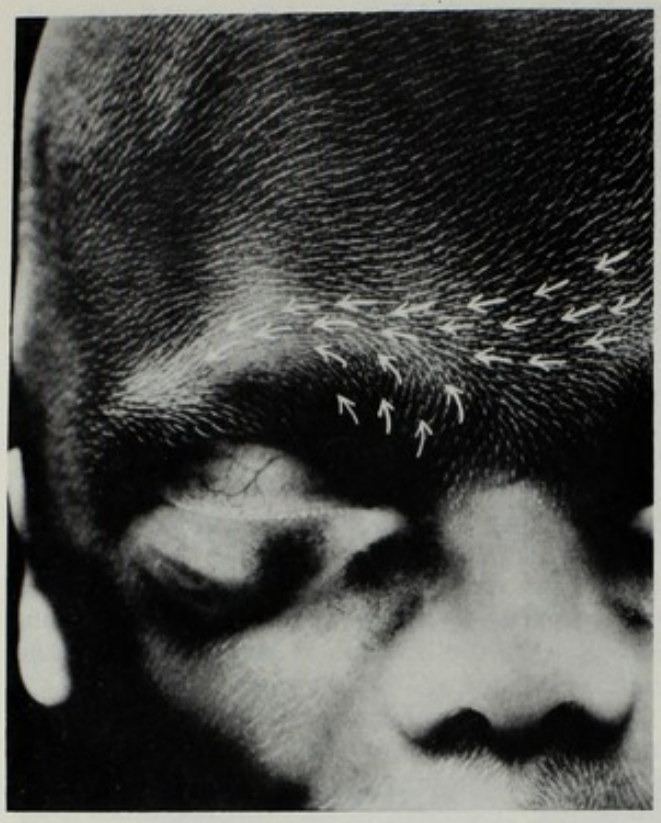


Figure 6.12. Frontal hair stream at 18 weeks arcing laterally from the ocular punctum to meet with the downsweeping parietal hair stream. The frontal hair stream has been influenced by the growth of the underlying upper facial structures and the forebrain. (From Smith, D. W., and Gong, B. T.: Teratology, *9*: 17, 1974.)

Hair Growth Patterns

Normal Development and Relevance. At 18 fetal weeks, when hair first emerges, it grows on the entire face and scalp, as noted in Figure 6.17. Later the eyebrows and scalp predominate, and the growth of hair over the remainder of the face is apparently suppressed. Studies imply that there is a periocular zone of hair growth suppression.

Nature and Relevance of Aberrant Facial Hair Growth Patterns. The V-shaped midline downward projection of the scalp hair, the widow's peak, is considered to represent an upper forehead intersection of the bilateral fields of periocular hair growth suppression. This may occur because the fields are widely spaced, as in ocular hypertelorism, or because the ocular fields of hair growth suppression are smaller with a low scalp hairline and low position of intersection, as illustrated in Figure 6.18. In the presence of cryptophthalmos there may be an abnormal projection of scalp-like hair growth toward the ocular area (Fig. 6.19).

The auricle appears to influence hair growth in the region anterior to the ear. With absence of the auricle there is usually absence of hair growth in the sideburn area (Fig. 6.20) anterior to the ear. With a rudimentary ear, such as is often found in the Treacher-Collins syndrome,

HAIR PATTERNING

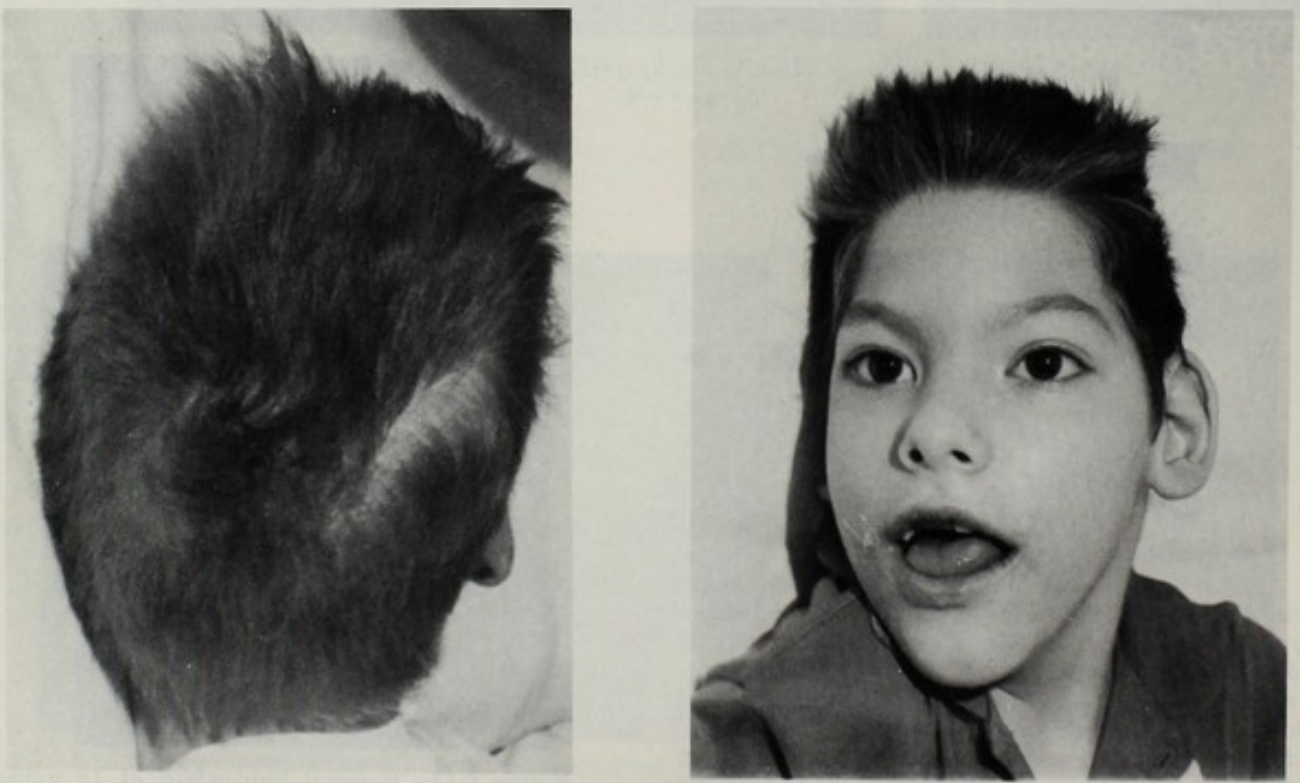


Figure 6.13. Hair patterning in a patient with primary microcephaly. The posterior scalp shows a lack of a concise whorl, and the anterior scalp shows a marked frontal upsweep. These findings are interpreted as being the consequence of a deficit in growth of the brain prior to and during the period of hair follicle development and thus imply an early defect in morphogenesis of the brain, prior to 10 to 16 weeks. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)



Figure 6.14. Posterior scalp hair patterning of the type more commonly found in mild microcephaly, in this instance, the Down syndrome. The parietal whorl tends to be more central and posterior than usual, being over the former position of the posterior fontanel. This is considered secondary to the brain having been smaller and more symmetric than usual at 10 to 16 weeks, the time when the hair follicles develop. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)

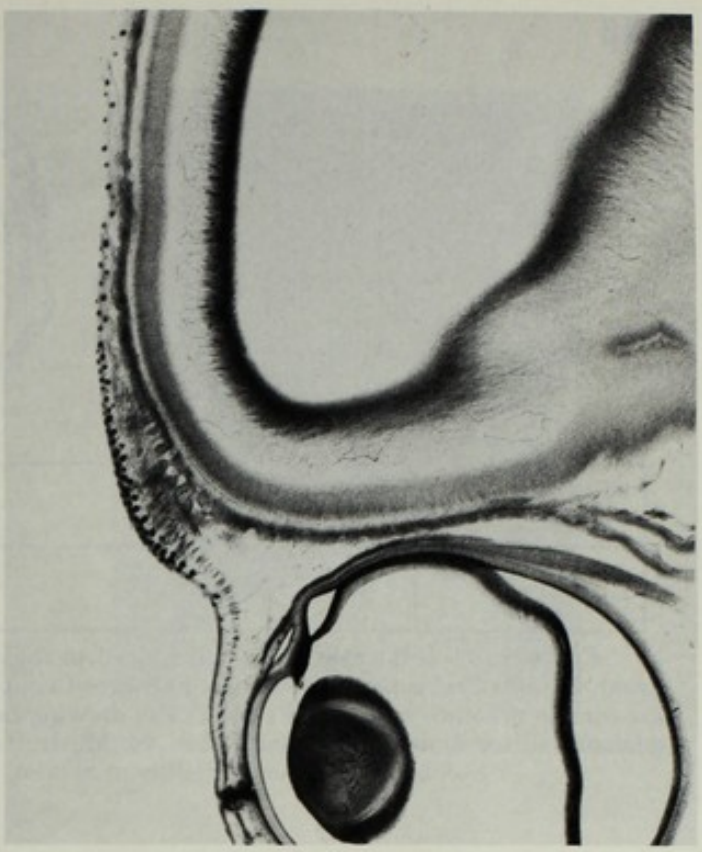


Figure 6.15. Sagittal section of forebrain area of a 10-week fetus showing the early stage of cerebral cortical development and the lack of any organized calvarium at the time the hair follicles are beginning their downgrowth. (From Smith, D. W., and Gong, B. T.: Teratology, *9*:17, 1974.)

HAIR PATTERNING



Figure 6.16. Aberrant mideyebrow patterning, which implies an aberration in growth and/or form of underlying facial structures by 10 to 16 fetal weeks. This patient has the Waardenburg syndrome, in which aberrant mid-upper facial development is a usual feature.

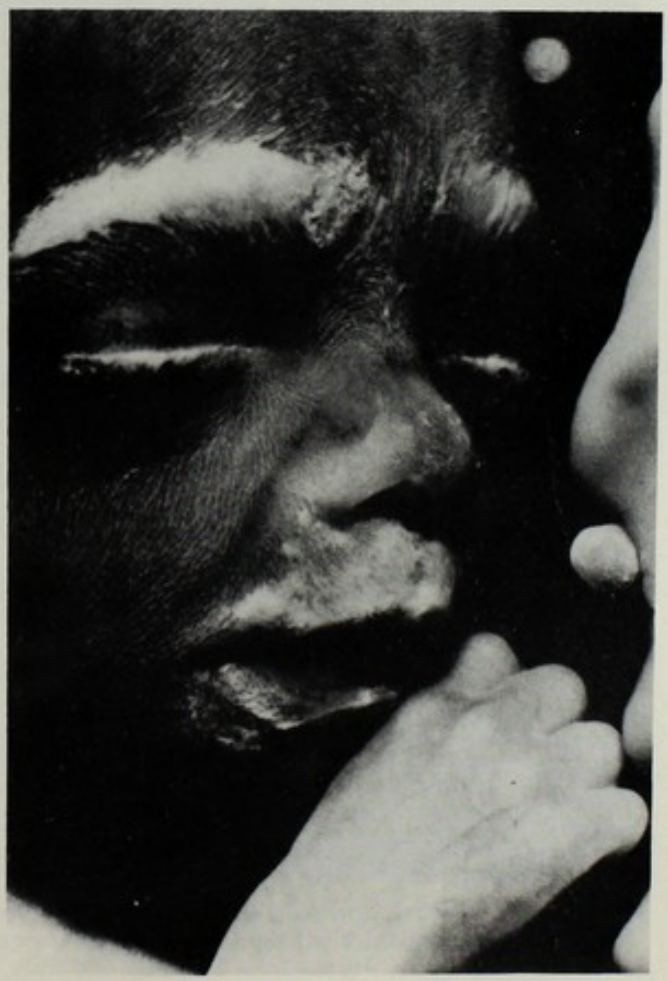


Figure 6.17. Hair growth on the face at 18 weeks, shortly after the hairs have been extruded onto the surface skin. (From Nilsson, L., Ingelman-Sundberg, A., and Wirsen, C.: A Child Is Born. New York, Delacorte Press, 1966.)



PERIOCULAR FIELDS	NORMAL	DECREASED	NORMAL
INTEROCULAR DISTANCE	NORMAL	NORMAL	INCREASED

Figure 6.18. If the eyes are widely spaced, or the area of periocular hair growth suppression is smaller than usual, the bilateral zones of periocular hair growth suppression may overlap at a lower point than usual, allowing for the presence of a widow's peak. The drawing on the right is of a patient with the frontonasal dysplasia anomaly. (From Smith, D. W., and Cohen, M. M., Jr.: Lancet, 2:1127, 1973.)

there may be an aberrant tongue of hair growth projecting onto the cheek area.

Usually short neck or webbed neck may be associated with the secondary feature of a low posterior hairline, especially at the lateral borders, as shown in Figure 6.21.

Whether the facial and body hirsutism (Fig. 6.22) found in patients with the de Lange syndrome and in a variety of failure to thrive growth deficiency disorders represents a more generalized failure of normal growth suppression in these conditions remains to be determined.

HAIR PATTERNING AND GROWTH



Figure 6.19. Aberrant growth of hair in lateral forehead area, related to the cryptophthalmos anomaly. (From Bergsma, D., and McKusick, V. A. (eds.): National Foundation – Birth Defects. Baltimore, Williams and Wilkins Co., 1973, p. 27.)

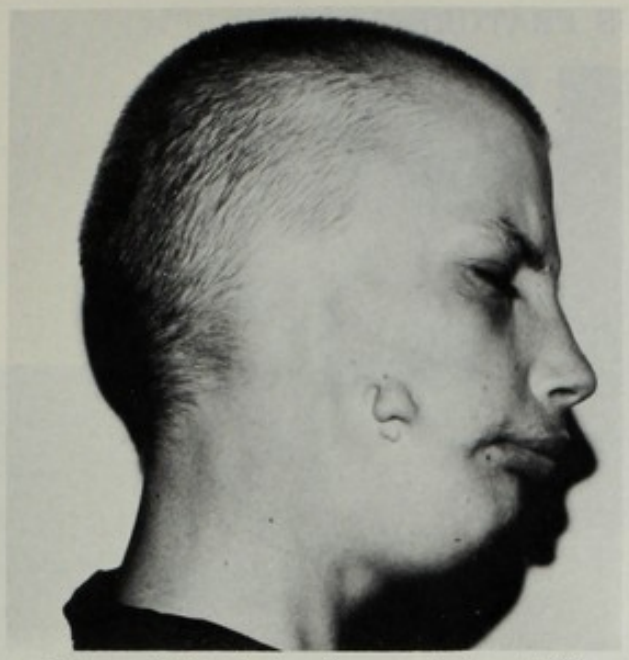


Figure 6.20. Lack of preauricular (sideburn) hair growth in relation to a deficit of auricular development.

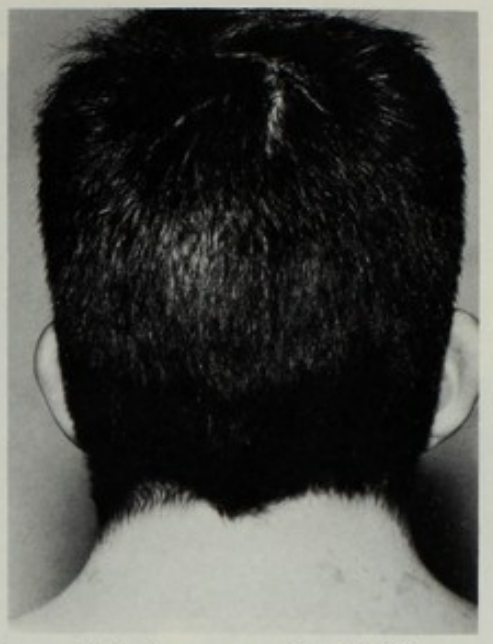


Figure 6.21. Low posterior hairline, usually related to either a short or webbed neck.

HAIR GROWTH

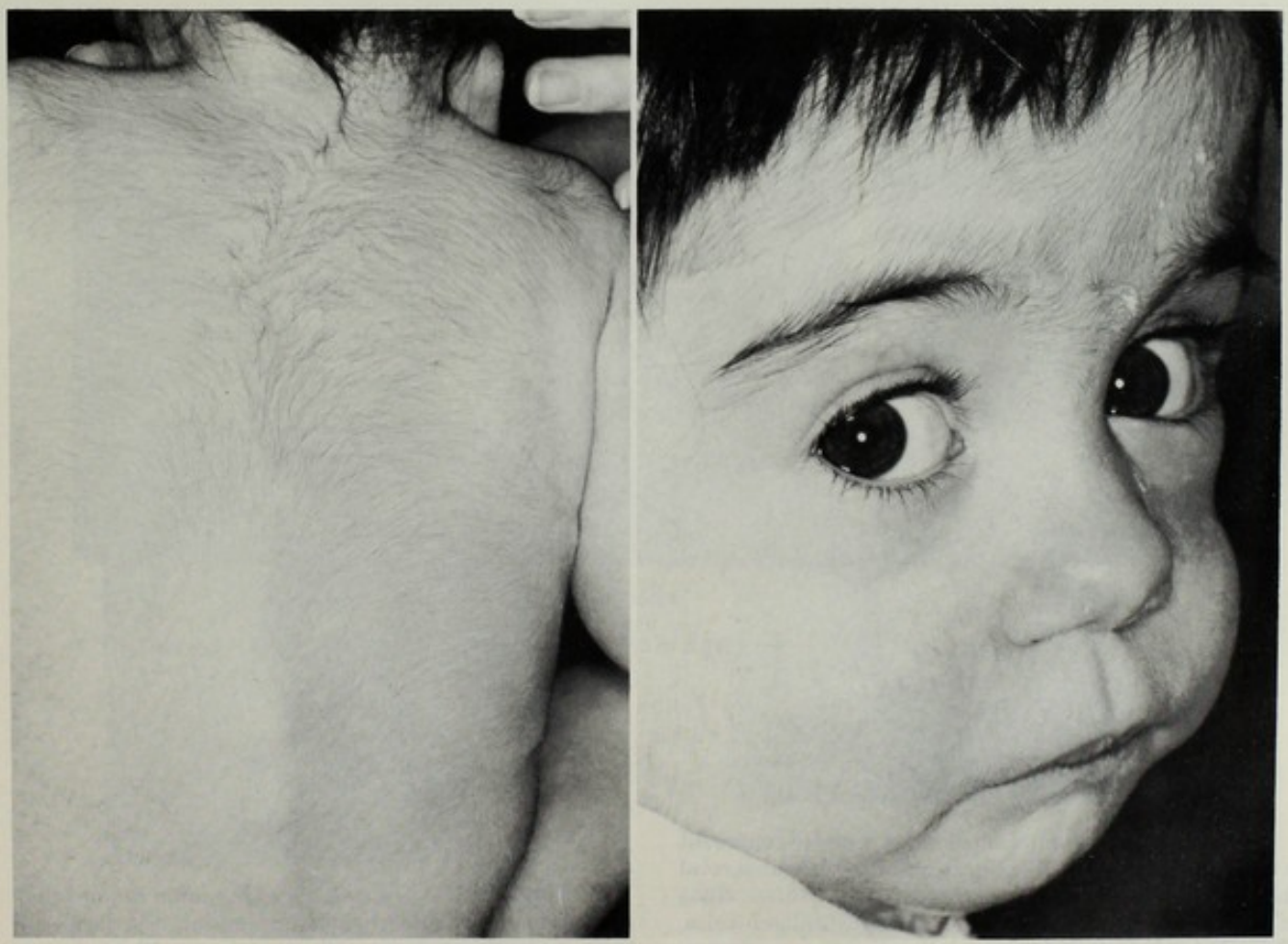


Figure 6.22. General facial and body hirsutism, presumably secondary to a general deficit in hair growth suppression in areas where the hair growth is usually suppressed, especially over the forehead and upper back.

OTHER CUTANEOUS FEATURES

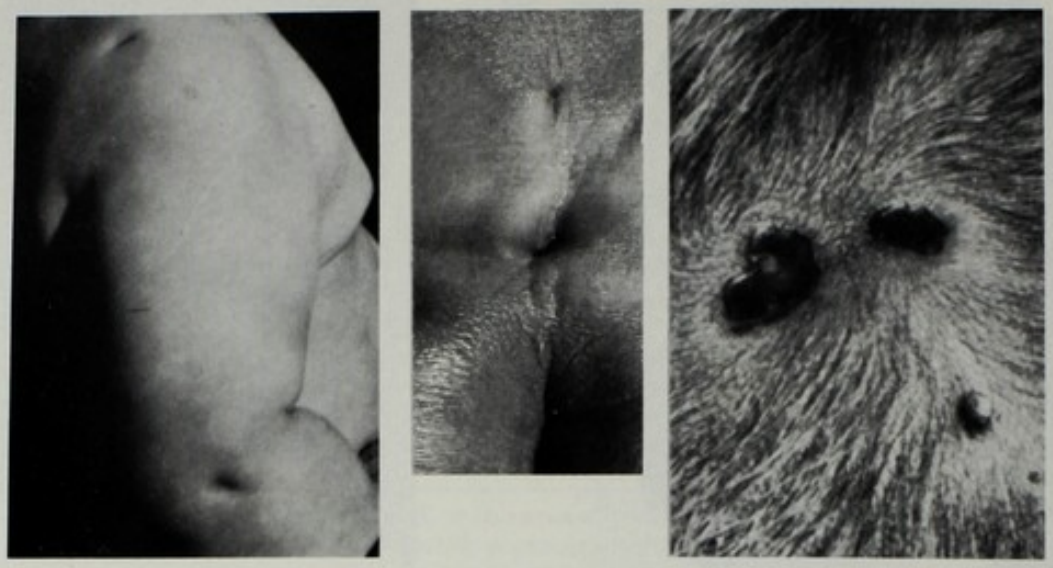


Figure 6.23. Unusual *dimples* may occur at a location where there has been a closer than usual proximity between the skin and underlying bony structures during fetal life, so that the development of subcutaneous tissue at that locus is deficient. Such dimples may either be secondary to a deficit in early subcutaneous tissue or to an aberrant bony promontory. They tend to occur at the elbows, knees, over the acromion promontories, and over the lower sacrum, as shown above. In the latter location they often have subsidiary creases and pits and should be distinguished from a pilonidal sinus.

Punched-out scalp lesions (right) are most commonly found toward the midline in the posterior parietal scalp area. The skin is usually totally lacking, but the crater becomes covered with scar tissue postnatally. The developmental pathology for these lesions is unknown.

GENITALIA

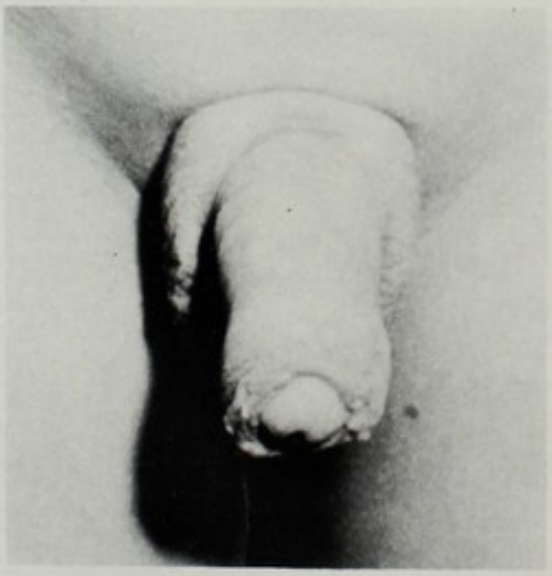


Figure 6.24. Shawl scrotum appears to represent a mild deficit in the full migration of the labial-scrotal folds and as such may be accompanied by other signs of incomplete masculinization of the external genitalia. This photo shows a patient with the Aarskog syndrome.

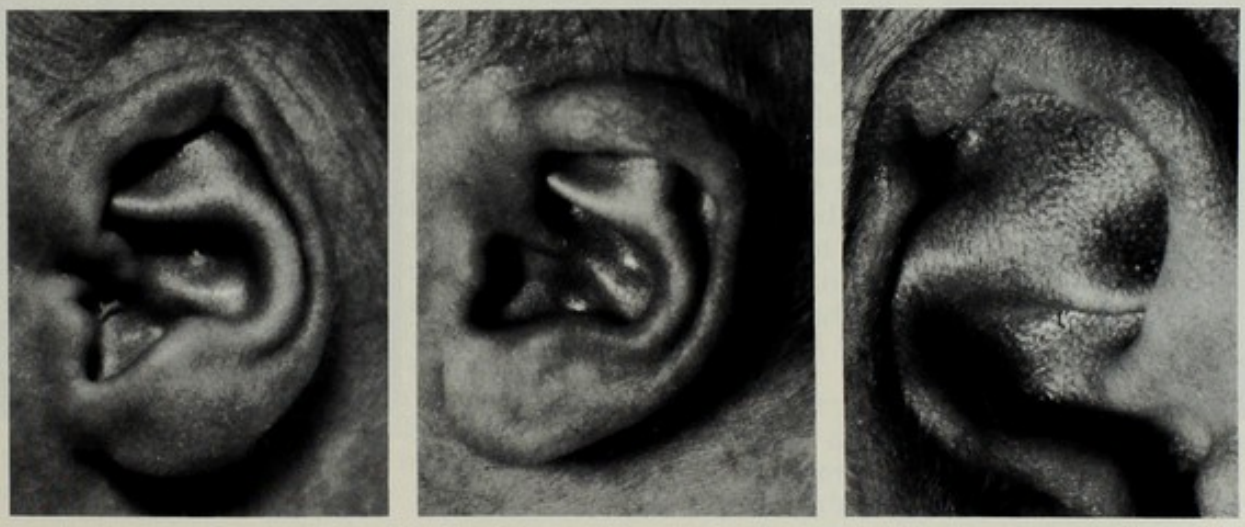


Figure 6.25. Hypoplasia of the labia majora may give rise to the false visual impression of a large clitoris, as in this patient with the trisomy 18 syndrome.

MINOR VARIANTS IN THE NEWBORN WHICH SHOULD *NOT* BE CLASSED AS ANOMALIES



Fine nonelevated pink to red capillary hemangiomata *(left to right)* at nape of neck, over central forehead and eyelids, and in lumbosacral area



Incompletely outfolded scapha helix

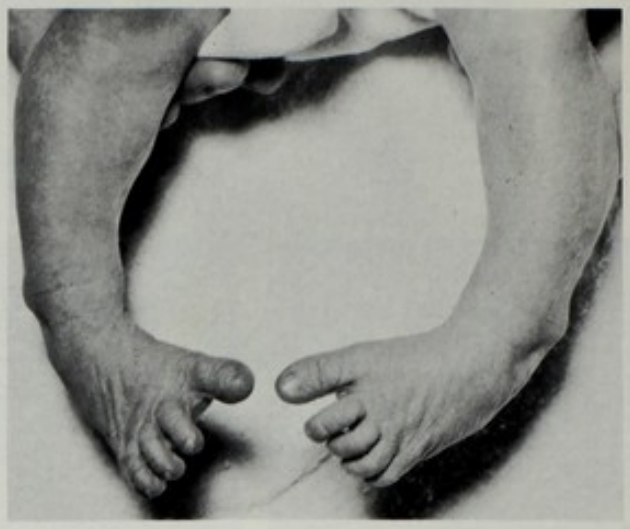
Darwinian tubercle

Figure 6.26.

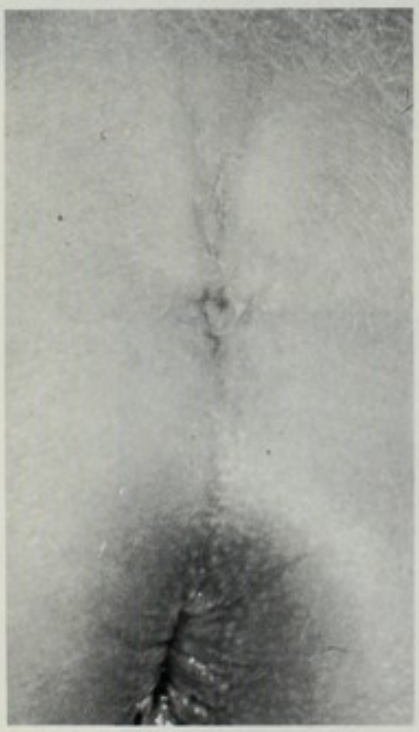
MINOR VARIANTS IN THE NEWBORN WHICH SHOULD *NOT* BE CLASSED AS MINOR ANOMALIES



"Saddle" nose, mildly upturned nares



Mild to moderate inbowing of lower leg with tibial torsion



Sacral dimple, not deep



Mild syndactyly of second and third toes; also toenail hypoplasia in newborn



Hydrocele of testicle

Figure 6.27.

REFERENCES

1. Marden, P. M., Smith, D. W., and McDonald, M. J.: Congenital anomalies in the newborn infant, including minor variations. J. Pediatr., *64*:357, 1964.
2. Popich, G. A., and Smith, D. W.: Fontanels: Range of normal size. J. Pediatr., *80*:479, 1972.
3. Smith, D. W., and Popich, G. A.: Large fontanels in congenital hypothyroidism: A potential clue toward earlier recognition. J. Pediatr., *80*:753, 1972.
4. Davies, P.: Sex and the single transverse crease in newborn singletons. Develop. Med. Child Neurol., *8*:729, 1966.
5. Popich, G. A., and Smith, D. W.: The genesis and significance of digital and palmar hand creases: Preliminary report. J. Pediatr., *77*:1917, 1970.
6. Mulvihill, J., and Smith, D. W.: Genesis of dermal ridge patterning. J. Pediatr., *75*:1969.
7. Ford-Walker, N.: Inkless methods of finger, palm and sole printing. J. Pediatr., *50*:27, 1957.
8. Uchida, I. A., and Soltan, H. C.: Evaluation of dermatoglyphics in medical genetics. Pediatr. Clin. North Am., *10*:409, 1963.
9. Aase, J. M. and Lyons, R. B.: Technique for recording dermatoglyphics. Lancet, *1*:432, 1971.
10. Smith, D. W., and Gong, B. T.: Scalp hair patterning as a clue to early fetal brain development. J. Pediatr., *83*:374, 1973; and Teratology, *9*:17, 1974.
11. Smith, D. W., and Cohen, M. M., Jr.: Widow's peak scalp anomaly, origin and relevance to ocular hypertelorism. Lancet, *2*:1127, 1973.

Chapter Seven

NORMAL STANDARDS

The following compilation of normal measurements is set forth as an aid in determining whether a given feature is abnormal or not. Such data may be especially useful when the visual impression is potentially misleading. For example, when the nasal bridge is low-set the visual impression may falsely suggest ocular hypertelorism, and when the patient is obese the hands may *appear* to be small. Besides comparing patient measurements to these normal cross-sectional population standards, it may be important to contrast the findings of the patient to those of his parents and/or siblings in an attempt to determine whether or not a given feature is unusual for that particular family.

These measurements have been predominantly obtained from Caucasians and hence may not be accurate for other racial groups. Separate data are presented for males and females, except for features which do not show significant differences between the sexes. For paired structures, the measurements are given for the right side. Many of the charts were kindly supplied by Dr. Murray Feingold from his recent Boston study of normal measurements.

STANDARDS FOR HEIGHT AND WEIGHT*

These were developed by J. M. Tanner and R. H. Whitehouse at the University of London Institute of Child Health. The following data relate to the first four growth charts for young children. The subsequent four growth charts from birth through adolescence are from Tanner, J. M., Whitehouse, R. H., and Takaishi, M.: Standards from birth to maturity for height, weight, height velocity, and weight velocity. Arch. Dis. Child., *41*:613, 1966.

Notes on Use

1. *Weight* is preferably taken in the nude; otherwise the estimated weight of clothing is subtracted before plotting.
2. When a child is born earlier than 40 weeks' gestation ("preterm") the birthweight is plotted at the appropriate number of weeks on the chart. Subsequent weights are plotted in relation to this "conception age"; thus for a child born at 32 weeks the 8 week-after-birth weight is plotted at B on the scale, the 12-week weight at 4 weeks after B and so on. Length is plotted in the same manner.
3. *Supine length* (up to age 2.0 years) should be taken with the infant lying on a measuring table constructed for this purpose.** One person holds the infant's head so that he looks straight upward (the lower borders of the eye sockets and the external auditory meati should be in the same vertical plane), and pulls very gently to bring the top of the head into contact with the fixed measuring board. A second person, the measurer, presses the infant's knees down into contact with the board, and, also pulling gently to stretch the infant out, holds the infant's feet, with the toes pointing directly upward. He brings the moveable footboard to rest firmly against the infant's heels and reads the measurement, to the last completed 0.1 cm.

*Obtainable from Creaseys Ltd., Print Division, Bull Plain, Hertford, England.

**Obtainable from Holtain Ltd., Crymmych, Pembrokeshire, England.

4. *Standing height* should be taken without shoes, the child standing with heels and back in contact with an upright wall, or preferably a stadiometer made for this purpose.** His head is held so that he looks straight forward, with the lower borders of the eye sockets in the same horizontal plane as the external auditory meati (i.e., head not with nose tipped upwards). A right-angled block (preferably counterweighted) is then slid down the wall until its bottom surface touches the child's head, and a scale fixed to the wall is read. During the measurement the child should be told to stretch his neck to be as tall as possible, though care must be taken to prevent his heels coming off the ground. Gentle but firm pressure upwards should be applied by the measurer under the mastoid processes to help the child stretch. In this way the variation in height from morning to evening is minimized. Standing height should be recorded to the last completed 0.1 cm.
5. The sources of the standards on young children are: (a) weight from 32 to 40 weeks gestation, Tanner-Thomson standards (published by Creaseys 1970 and in Arch. Dis. Child., *45*:566, 1970) from Aberdeen data; (b) length from 32–40 weeks estimated from West European and North American data, not available for England; (c) weight and length after 40-week birth, same sources as Tanner-Whitehouse 0–18 year old standards (published by Creaseys 1966 and detailed in Arch. Dis. Child., *41*:454, 613, 1966.)

LINEAR GROWTH
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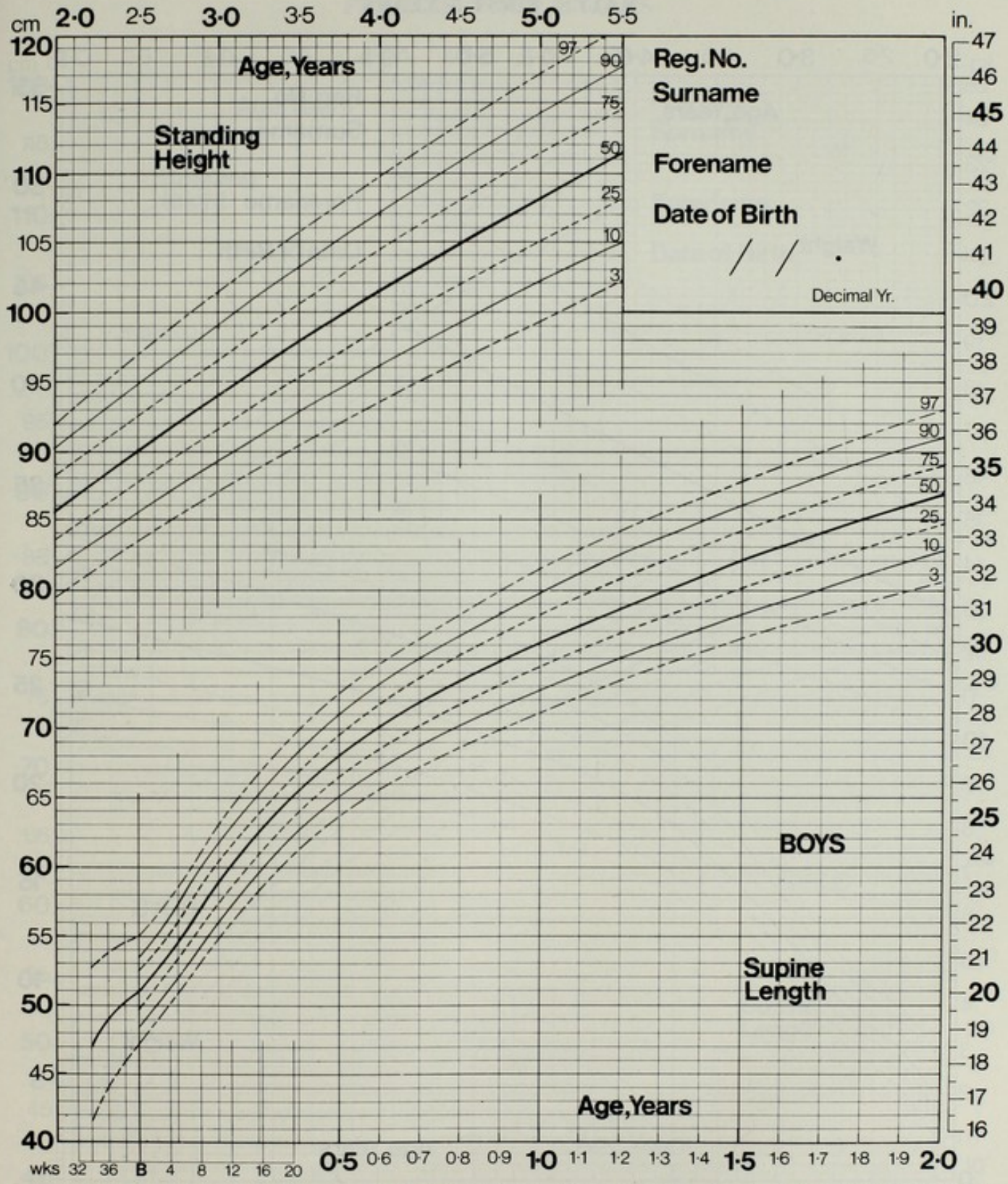
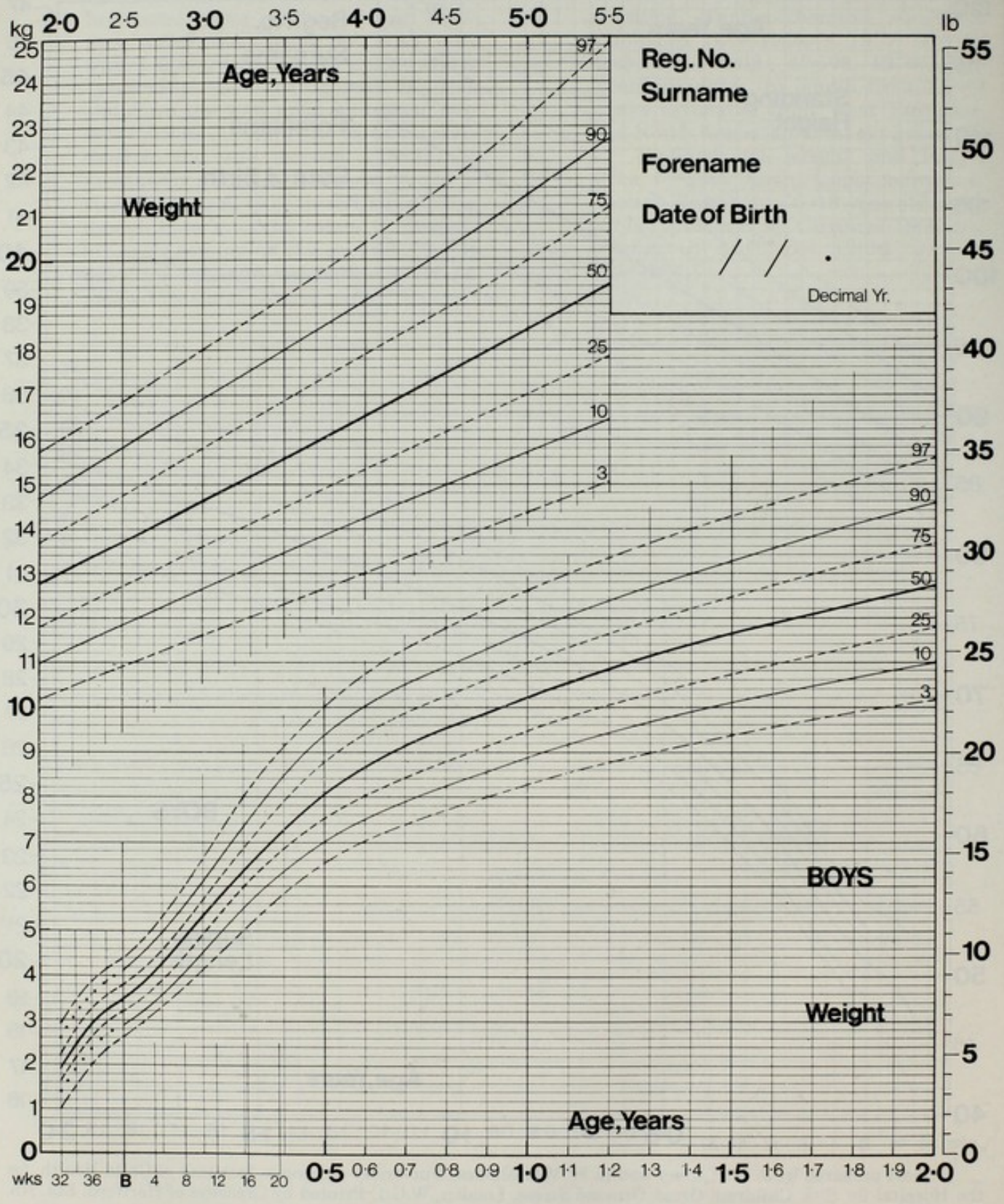
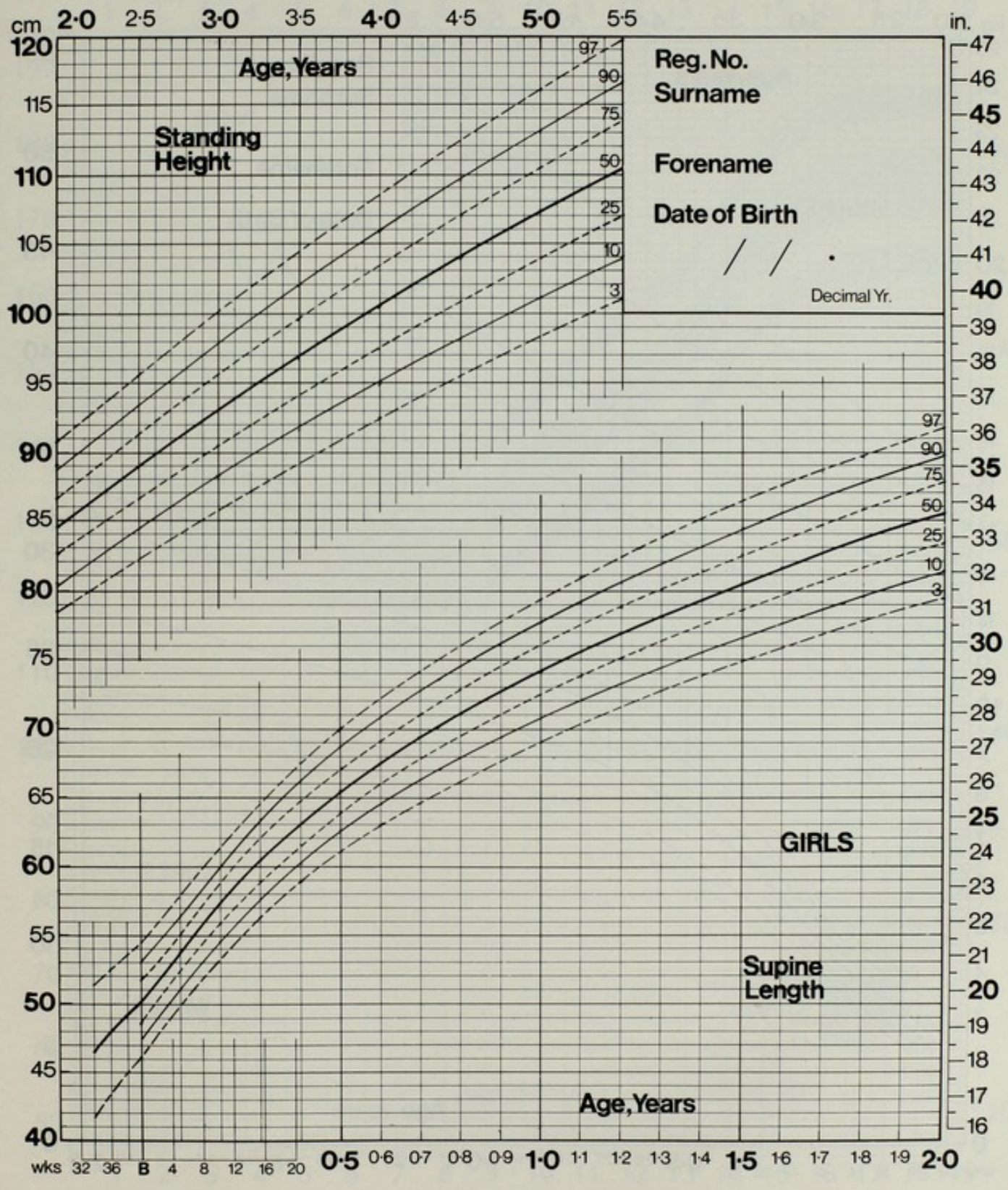


Chart prepared by J. M. Tanner and R. H. Whitehouse, University of London Institute of Child Health, for the Hospital for Sick Children, Great Ormond Street, London, W.C.1. Printed by Creaseys of Hertford, Ltd. No. Ref SHWB28.

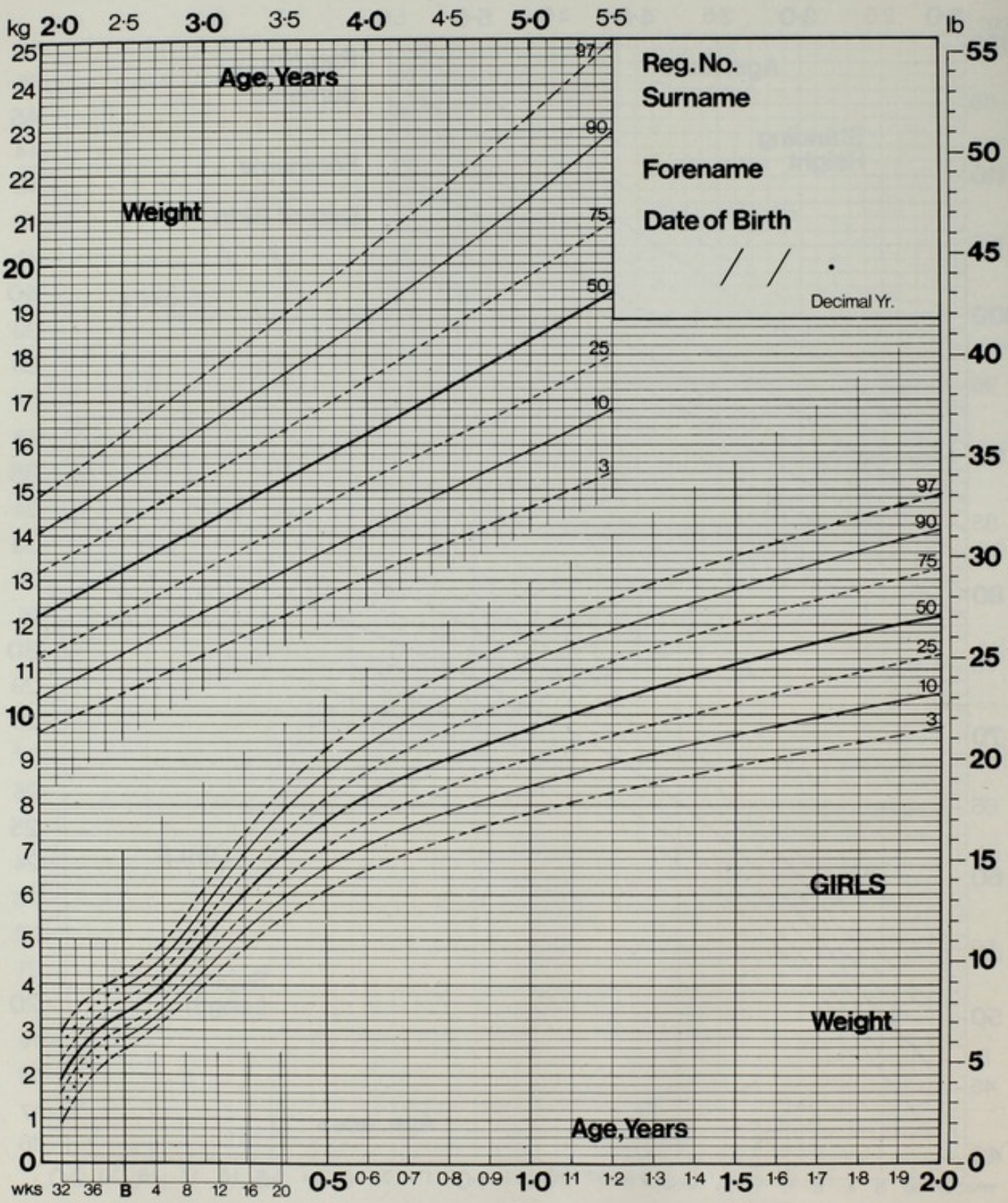
WEIGHT GROWTH
MALES, FIRST 5 YEARS



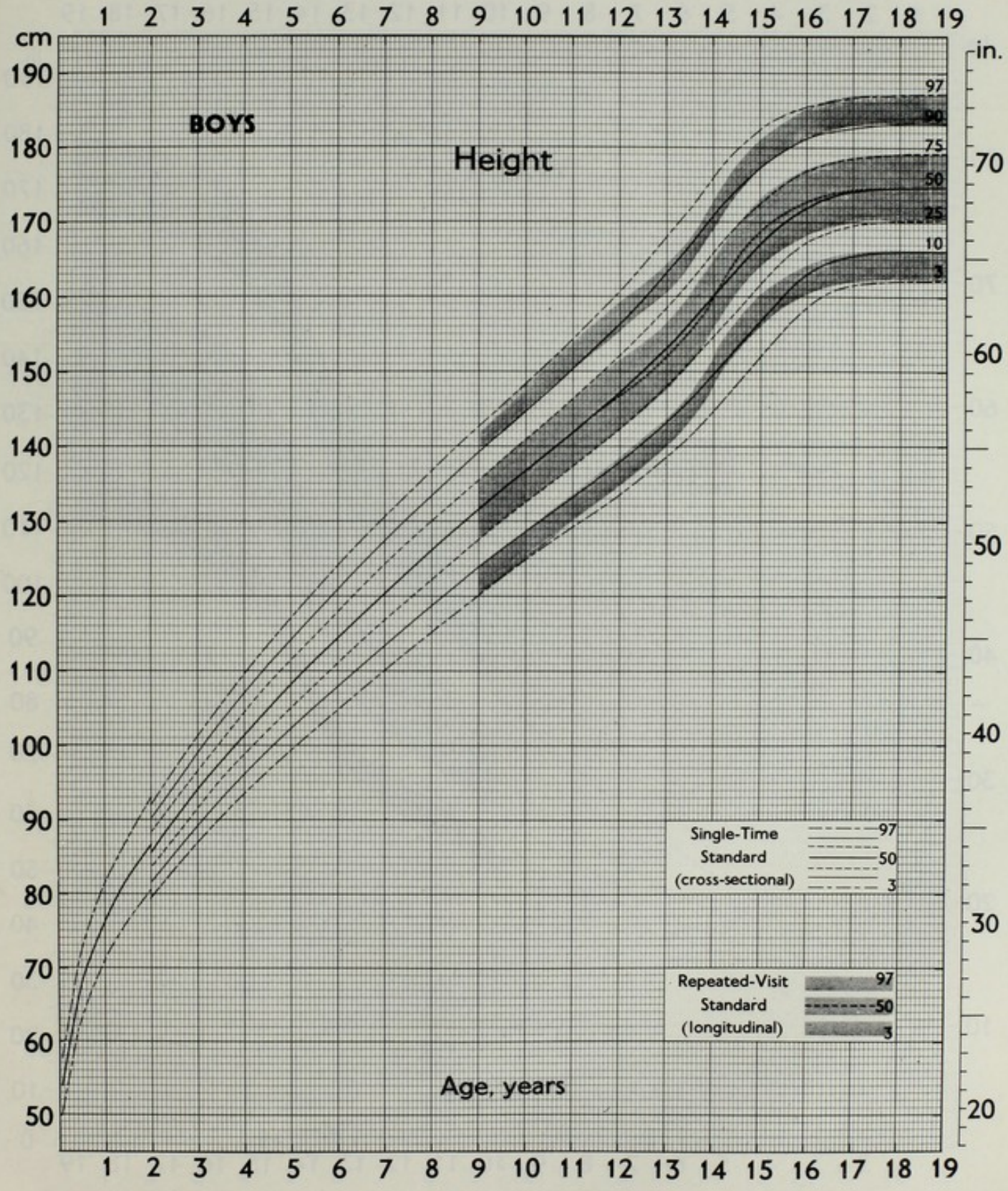
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FEMALES, FIRST 5 YEARS



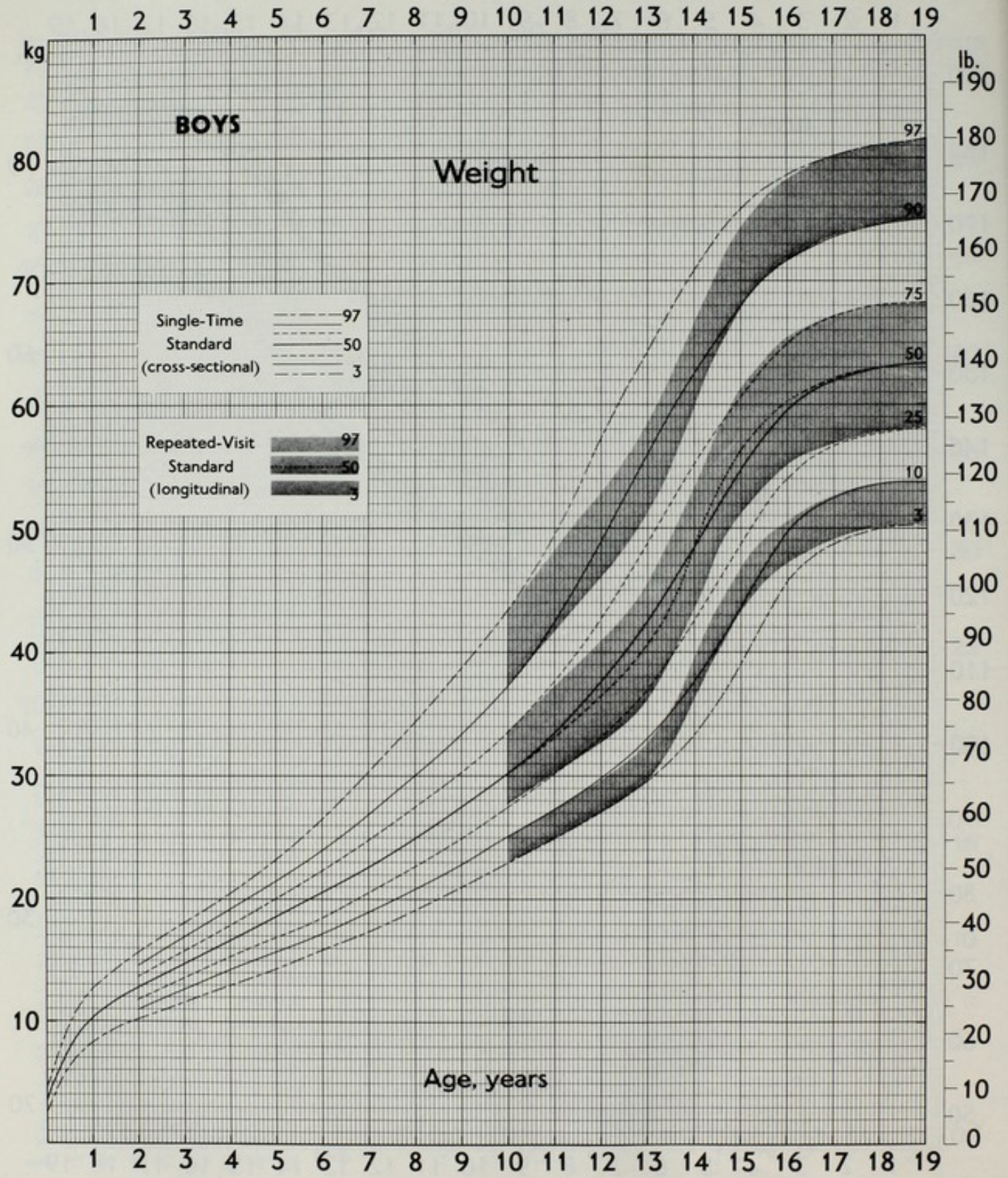
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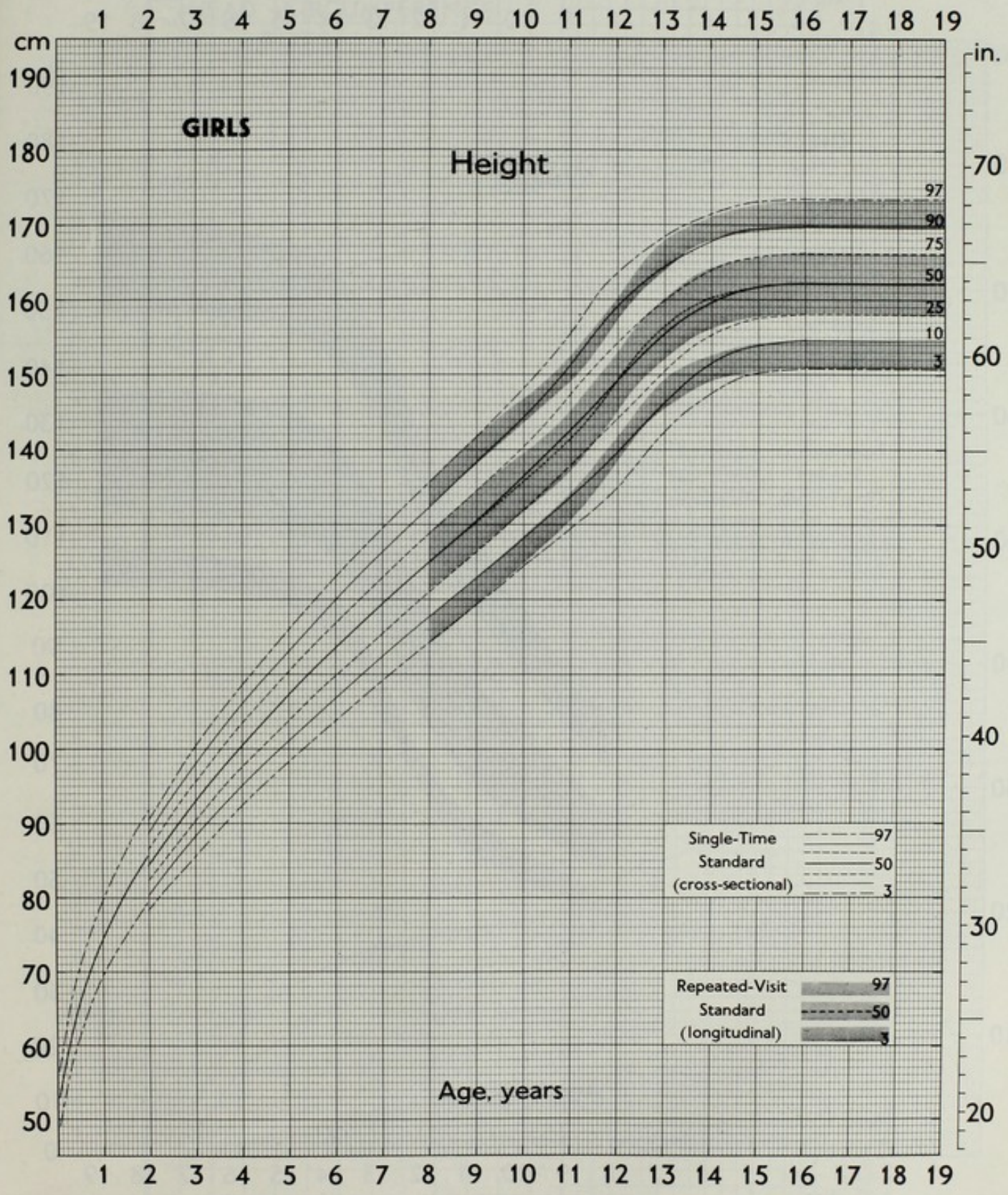
LINEAR GROWTH
MALES



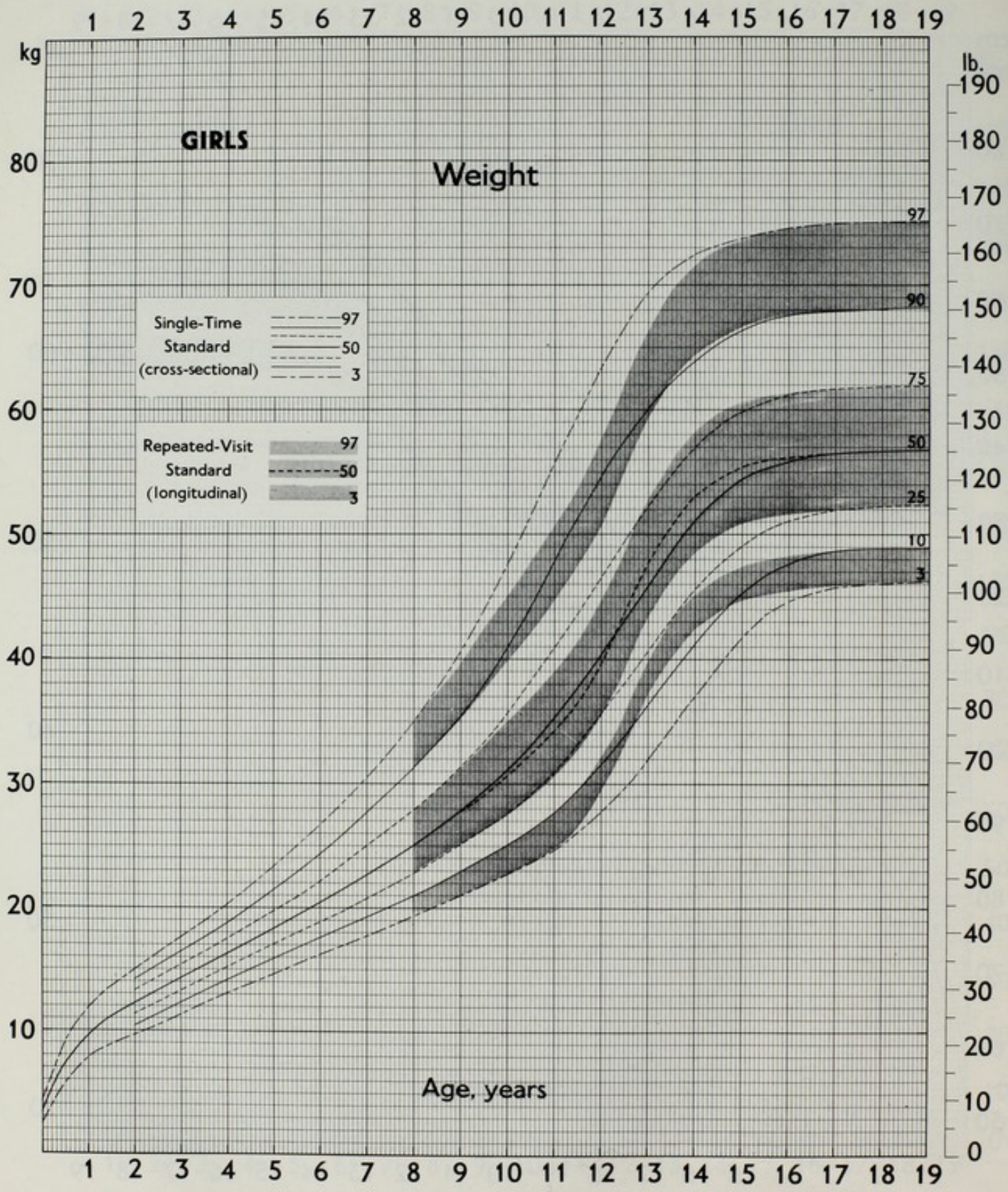
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MALES



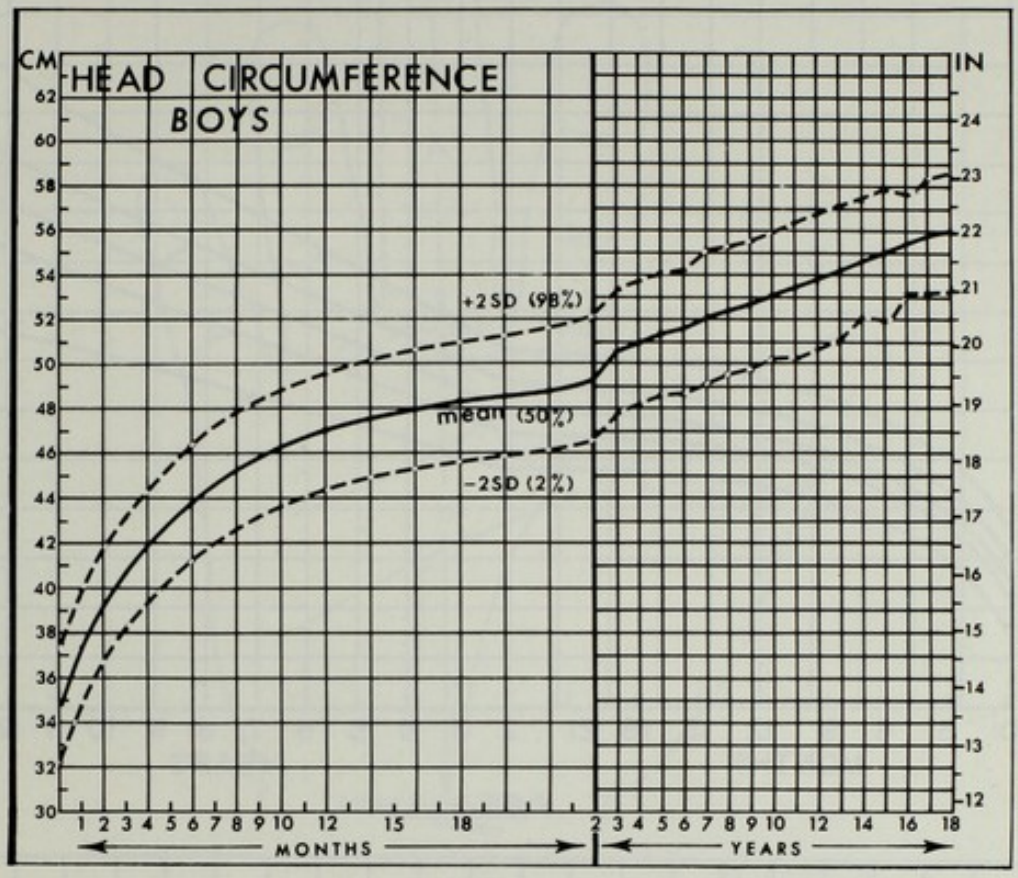
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FEMALES

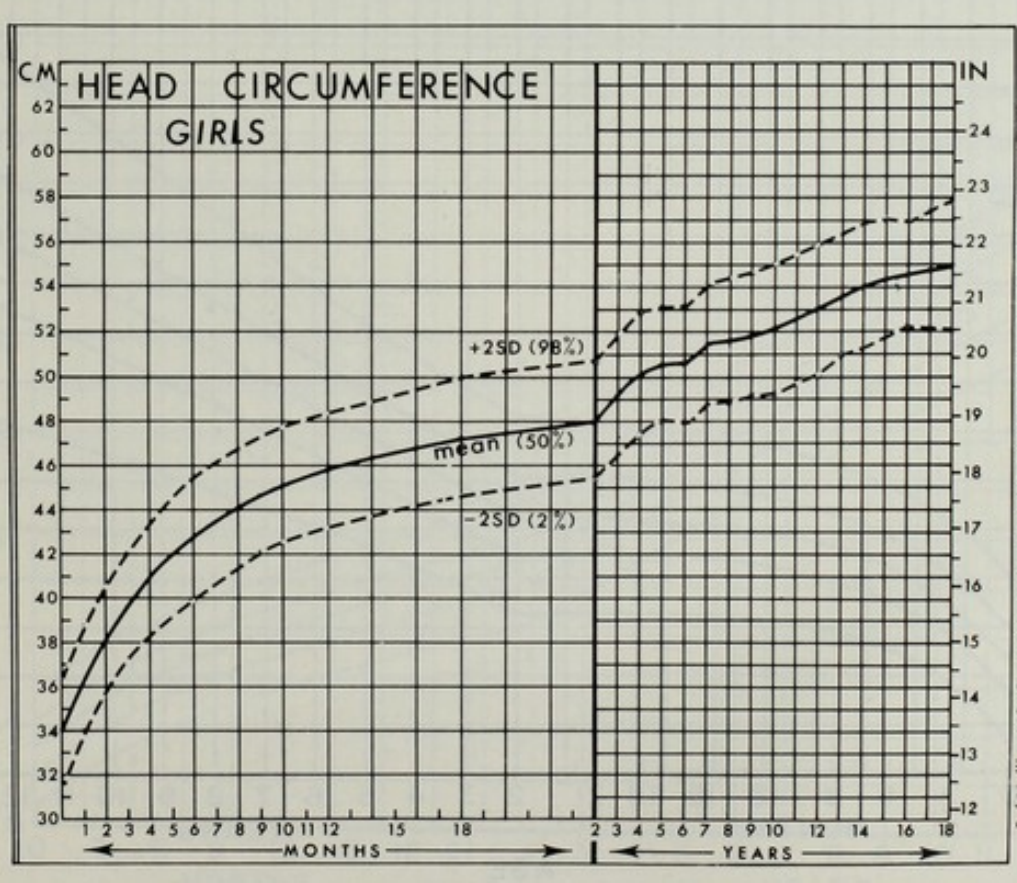


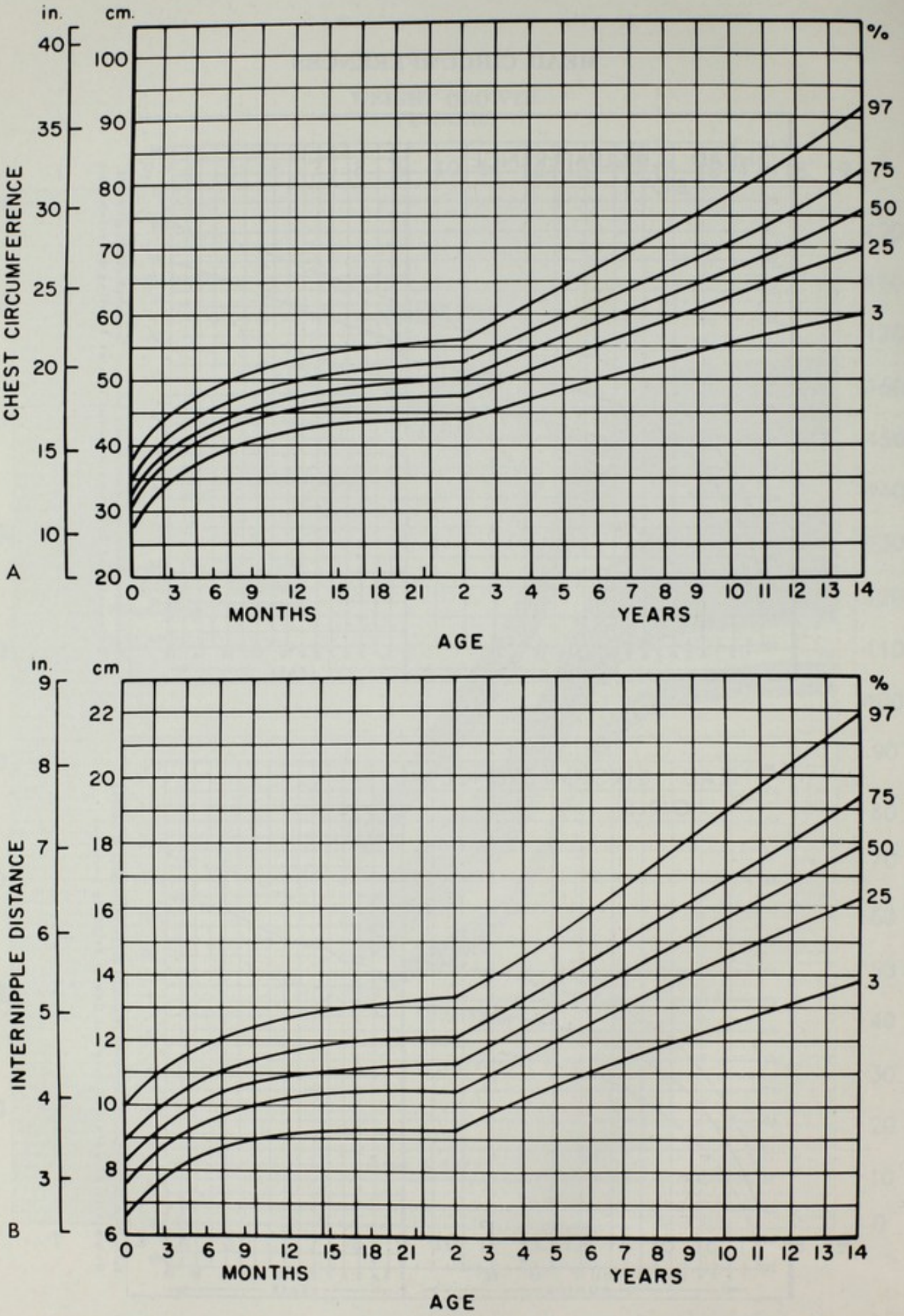
WEIGHT GROWTH
FEMALES



HEAD CIRCUMFERENCES

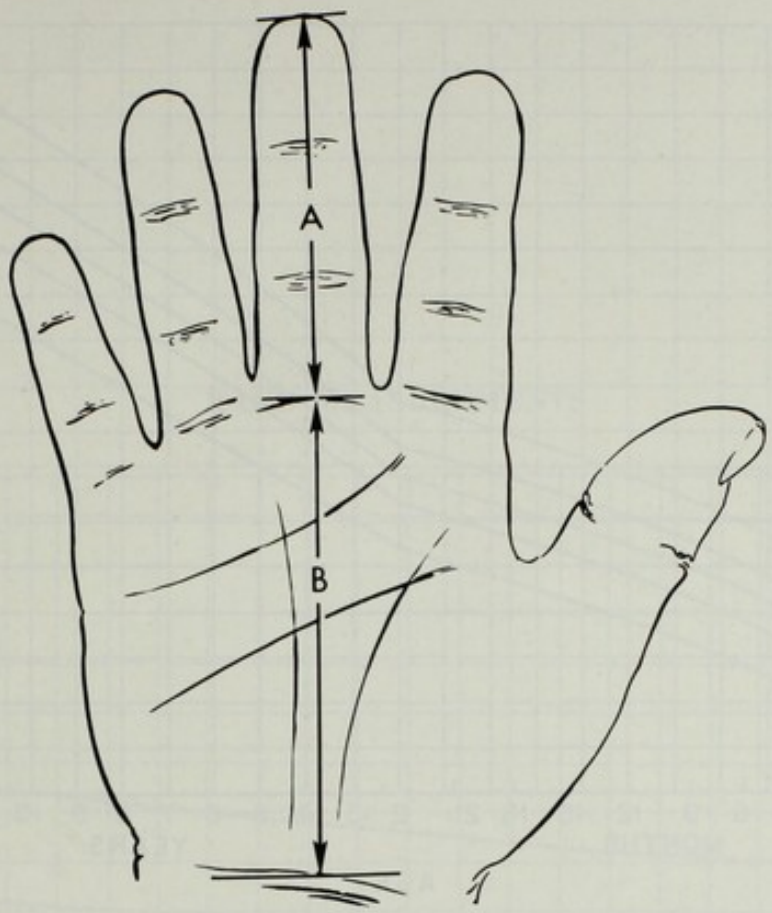


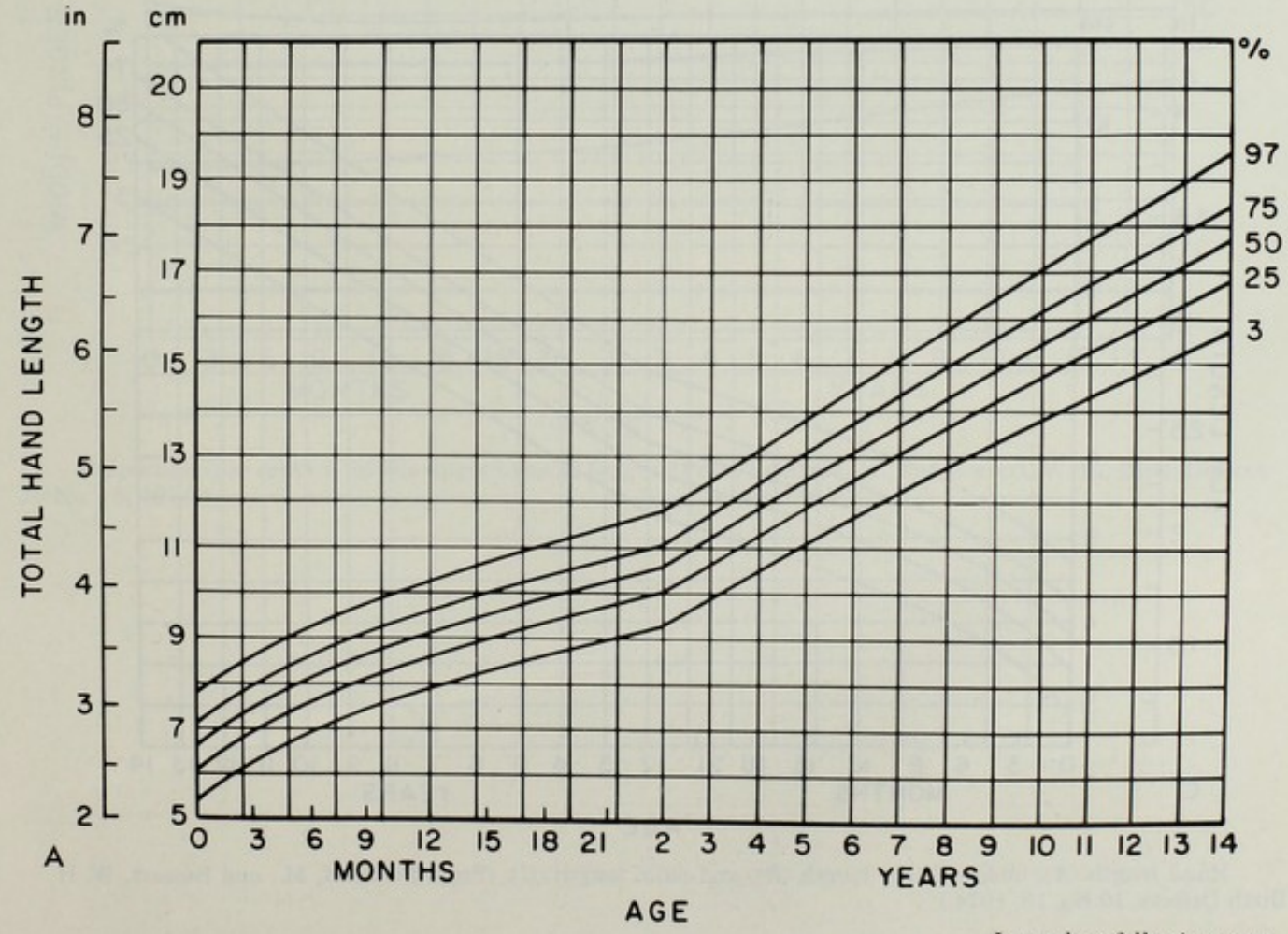




Chest circumference (*A*) and internipple distance (*B*). (From Feingold, M., and Bossert, W. H.: Birth Defects, *10*:No. 13, 1974.)

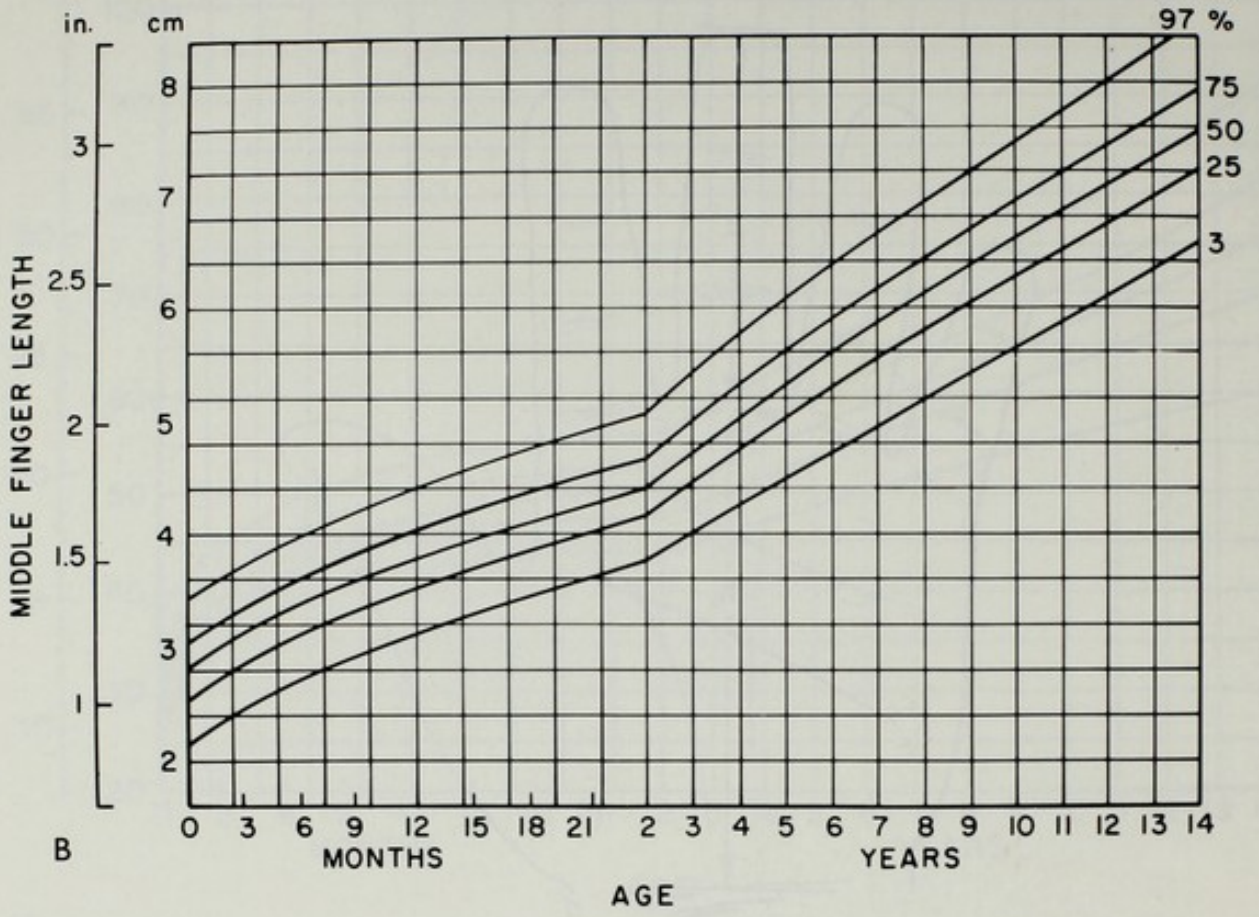
HAND MEASUREMENTS

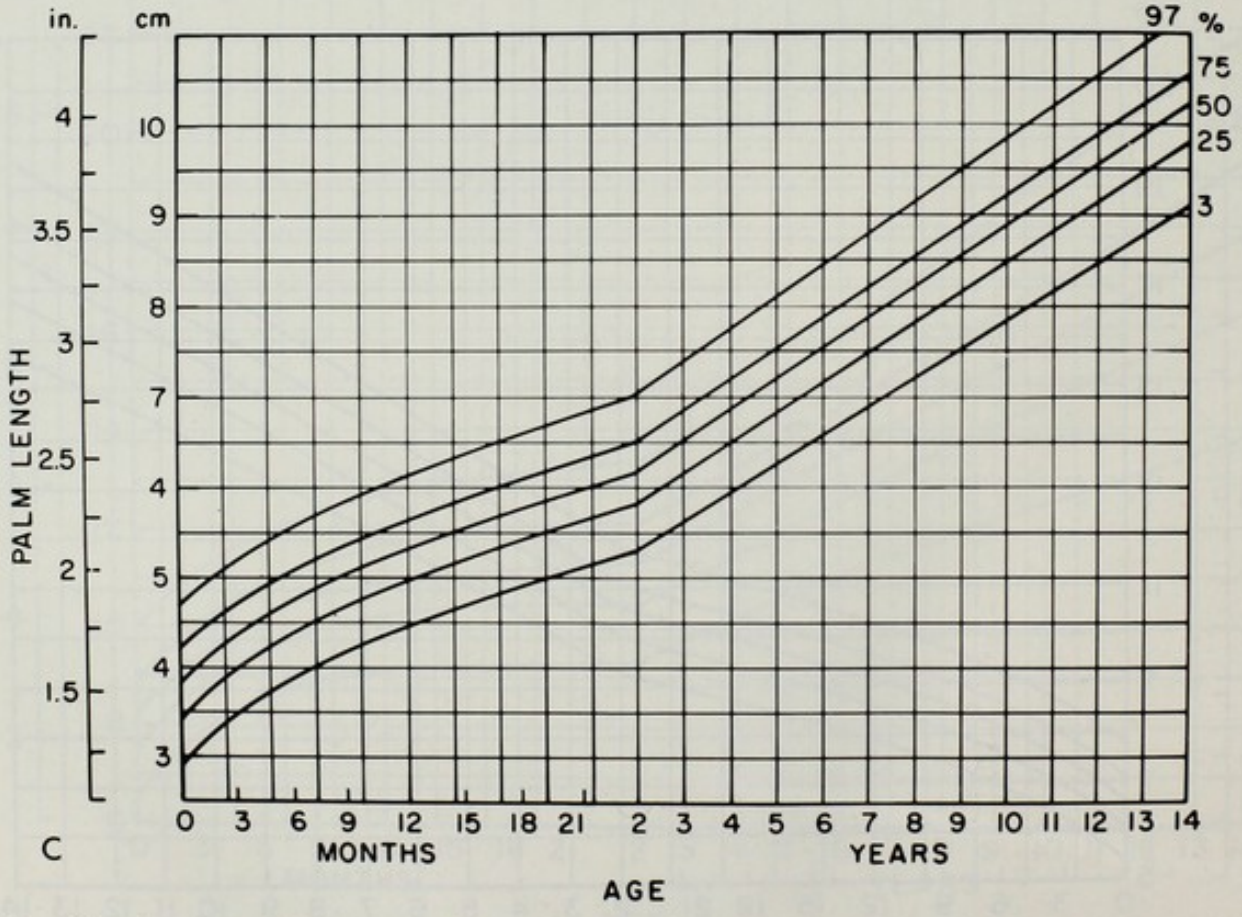




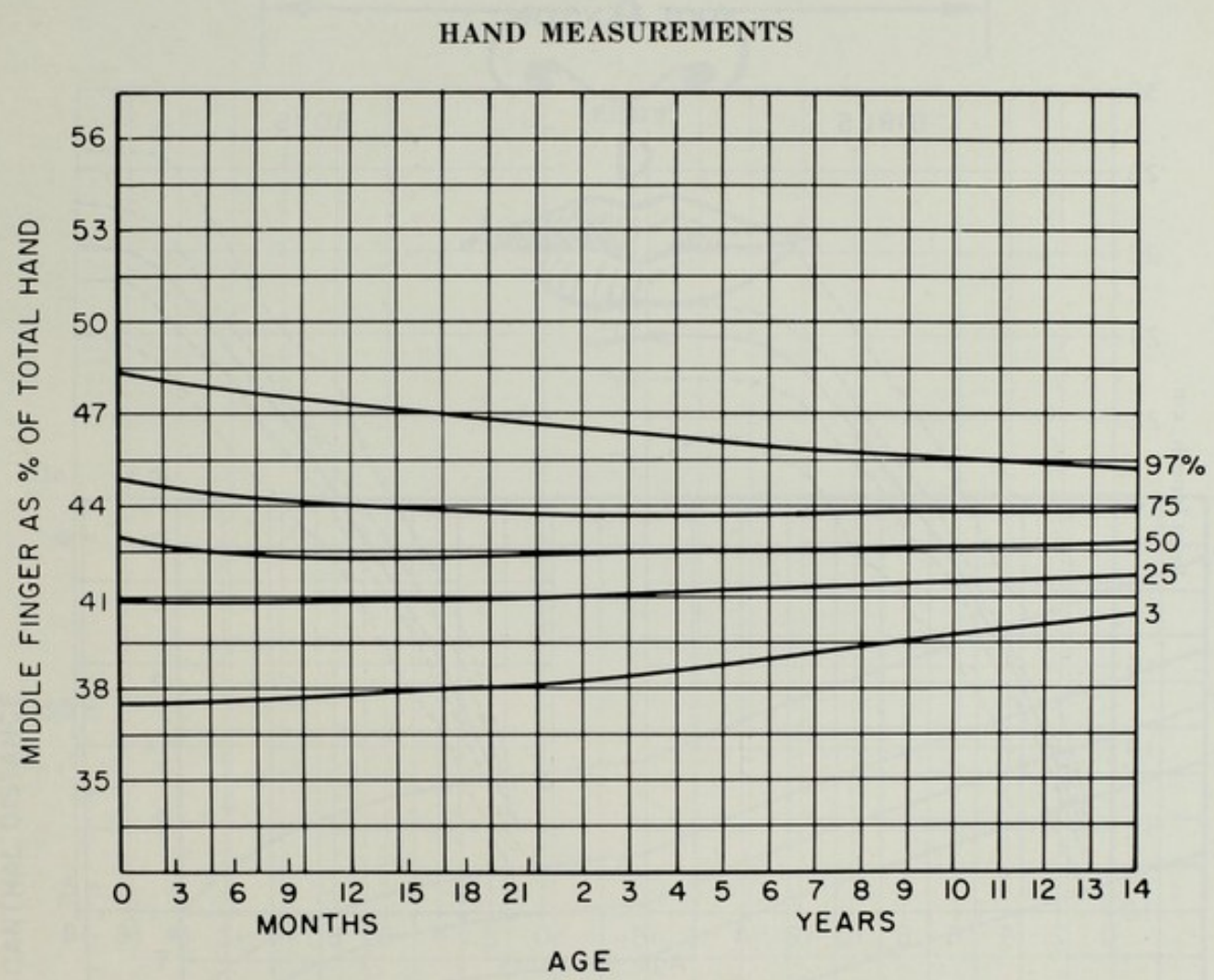
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HAND MEASUREMENTS



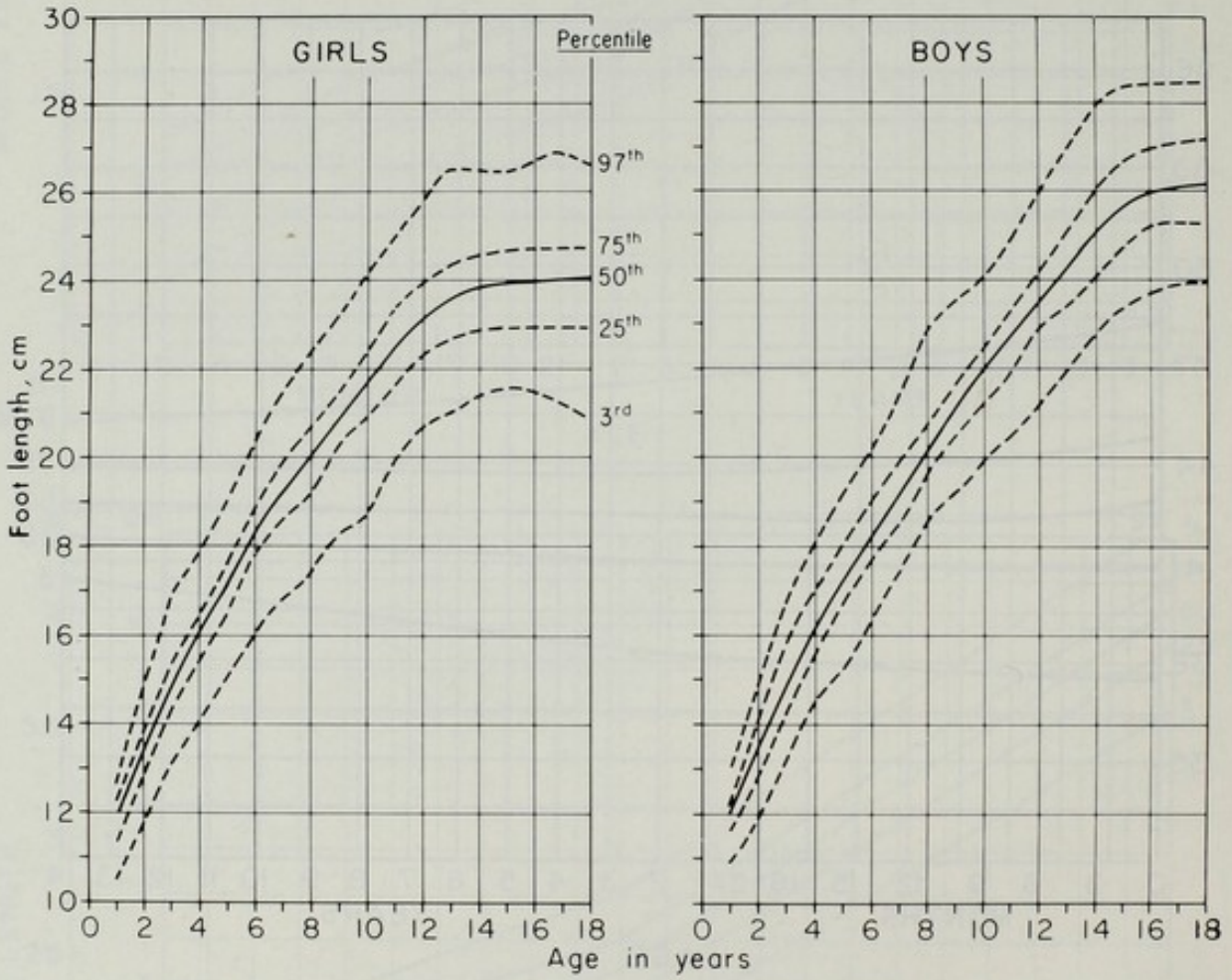


Hand length (*A*), middle finger length (*B*), and palm length (*C*). (From Feingold, M., and Bossert, W. H.: Birth Defects, *10*:No. 13, 1974.)



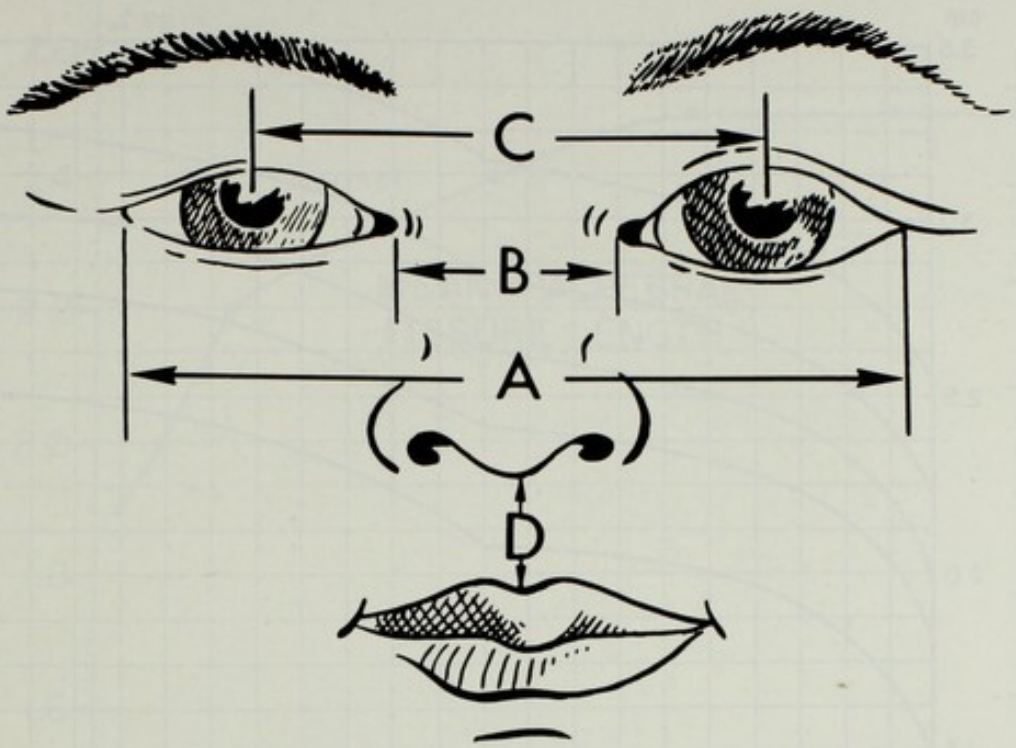
Proportion (per cent) of middle finger to hand length. (From Feingold, M., and Bossert, W. H.: Birth Defects, *10*:No. 13, 1974.)

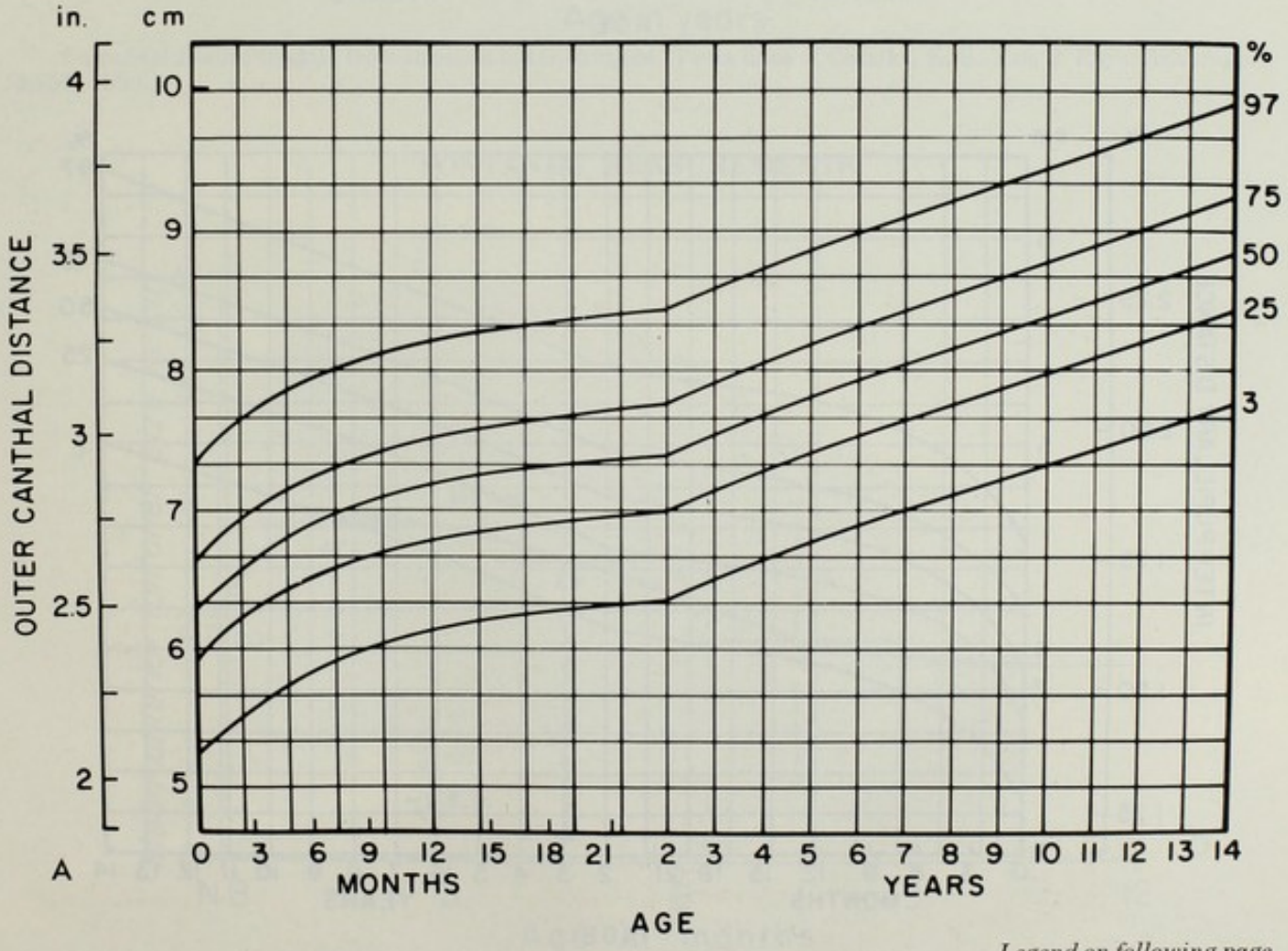
FOOT LENGTH



Mean and percentile values for foot length. Note: The adolescent growth spurt of the foot usually begins prior to the general linear growth spurt and ends before final height attainment. Thus, the foot growth spurt is a good early indicator of adolescence. (Adapted from Blais, M. M., Green, W. T. and Anderson, M.: J. Bone Joint Surg., *38-A*:998, 1956.)

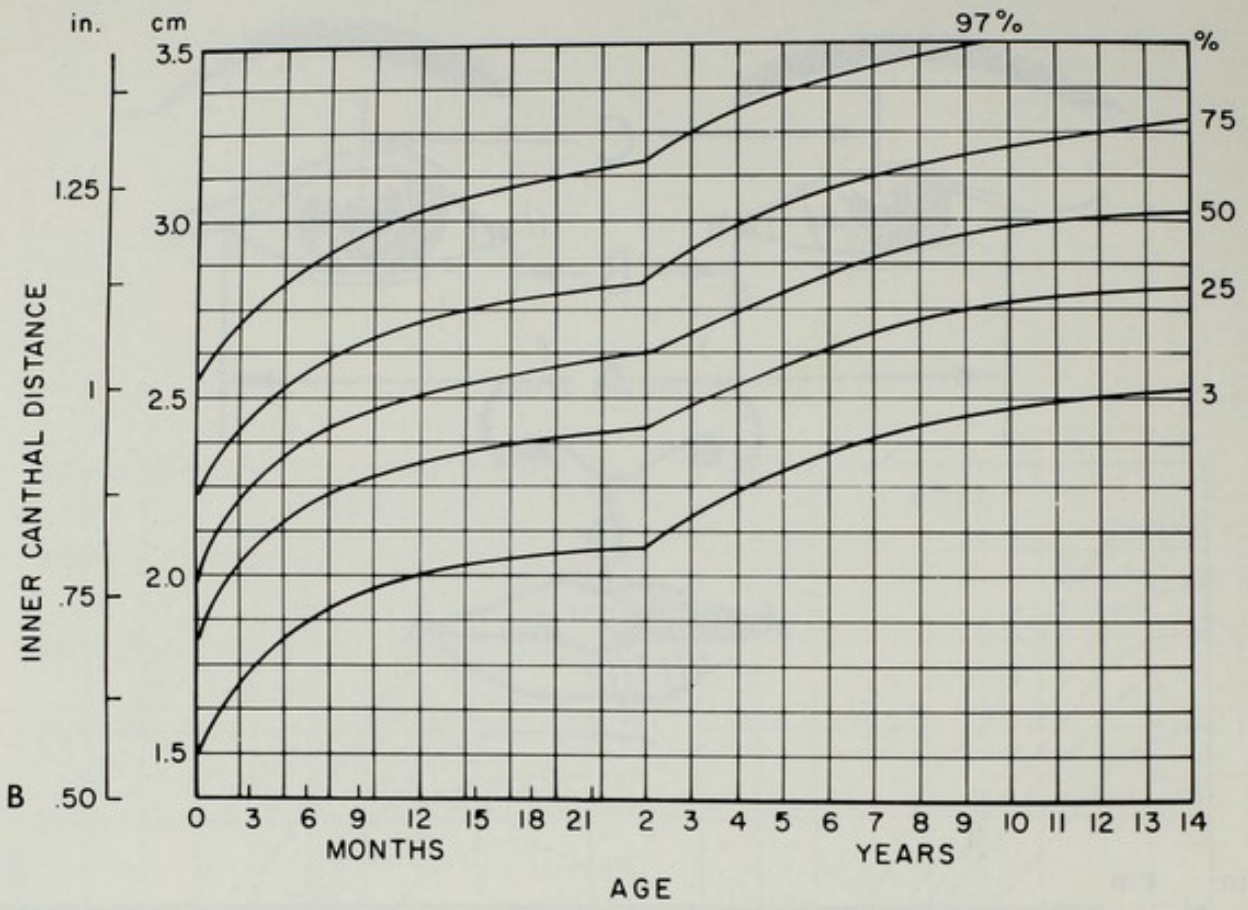
FACIAL MEASUREMENTS

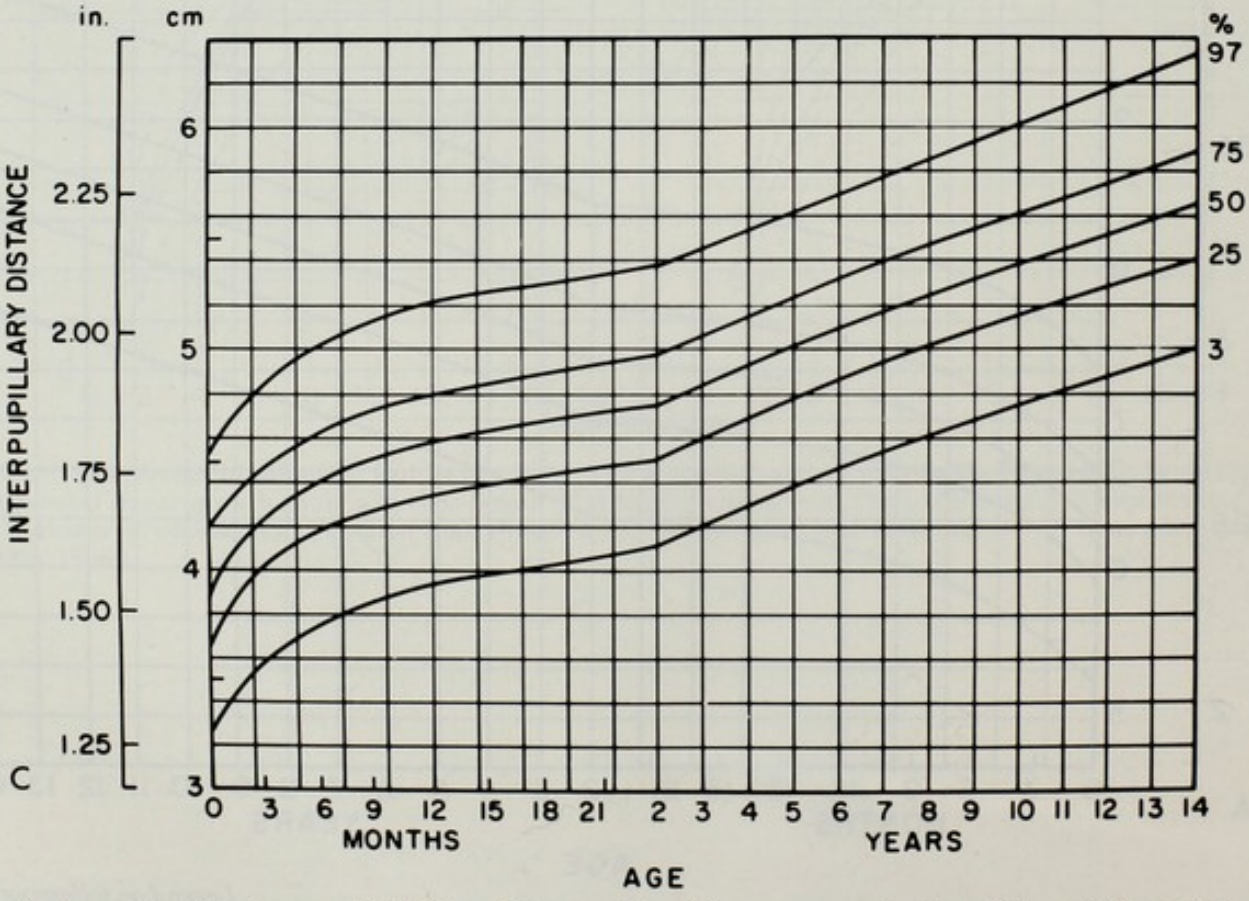




Legend on following page

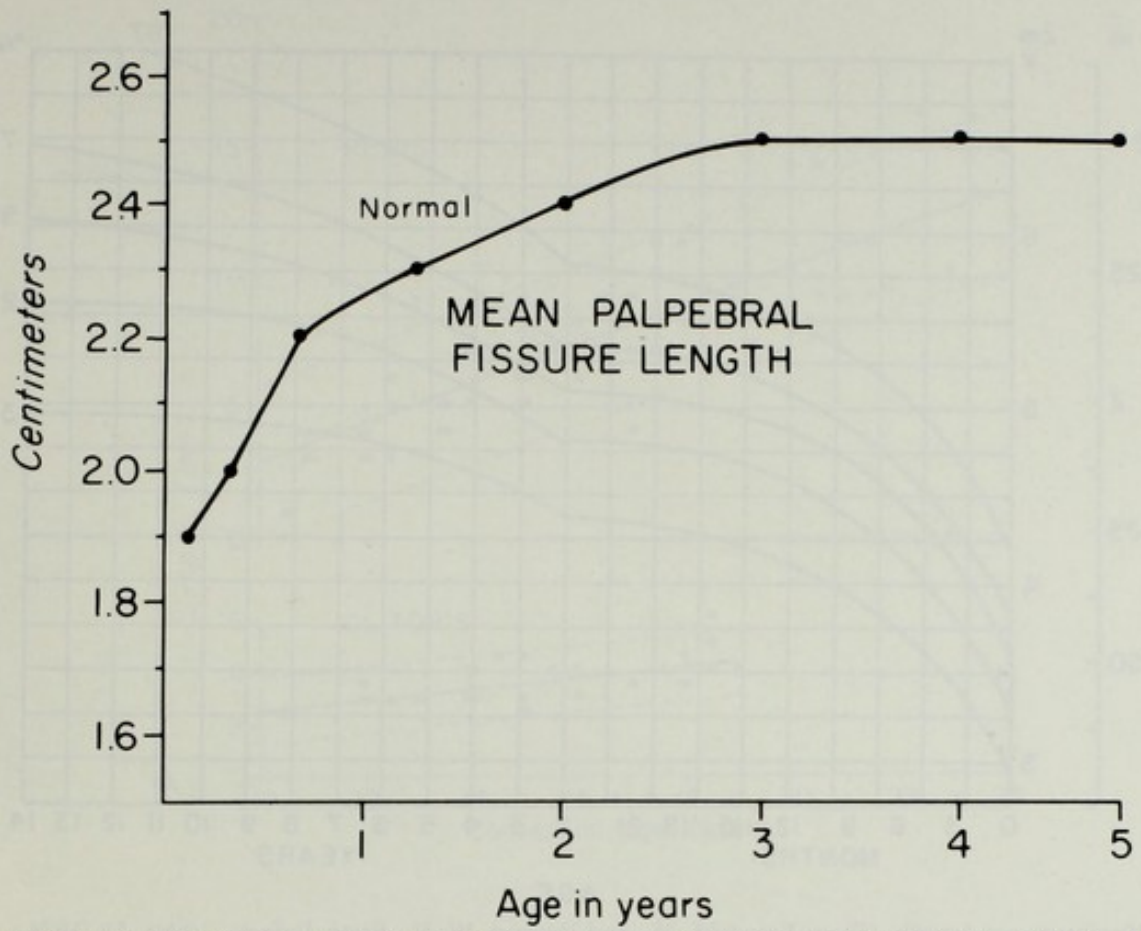
FACIAL MEASUREMENTS





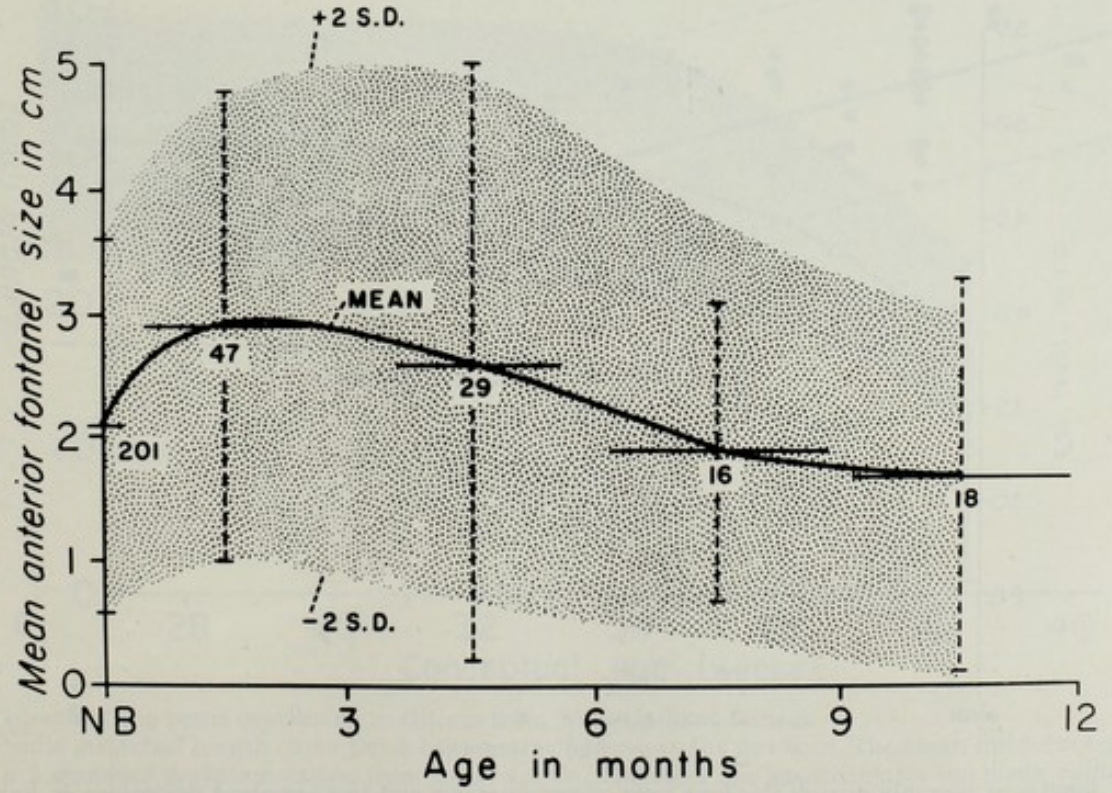
Outer canthal (*A*), inner canthal (*B*), and interpupillary (*C*) measurements. (From Feingold, M., and Bossert, W. H.: Birth Defects, *10*:No. 13, 1974.)

FACIAL MEASUREMENTS



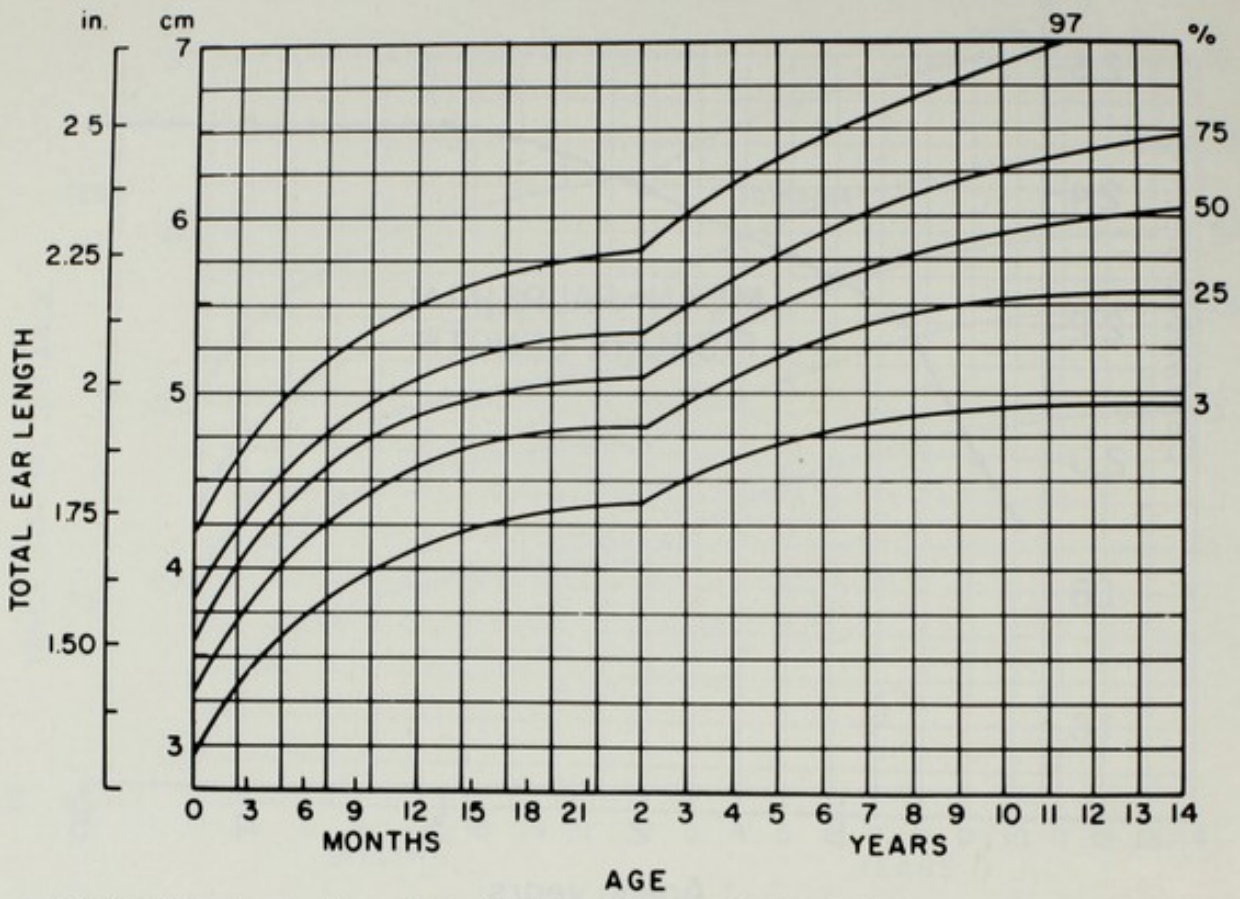
Palpebral fissure length, from inner to outer canthus. (From data of Chouke, K. S.: Am. J. Phys. Anthropol., *13*:255, 1929.)

FONTANEL MEASUREMENTS

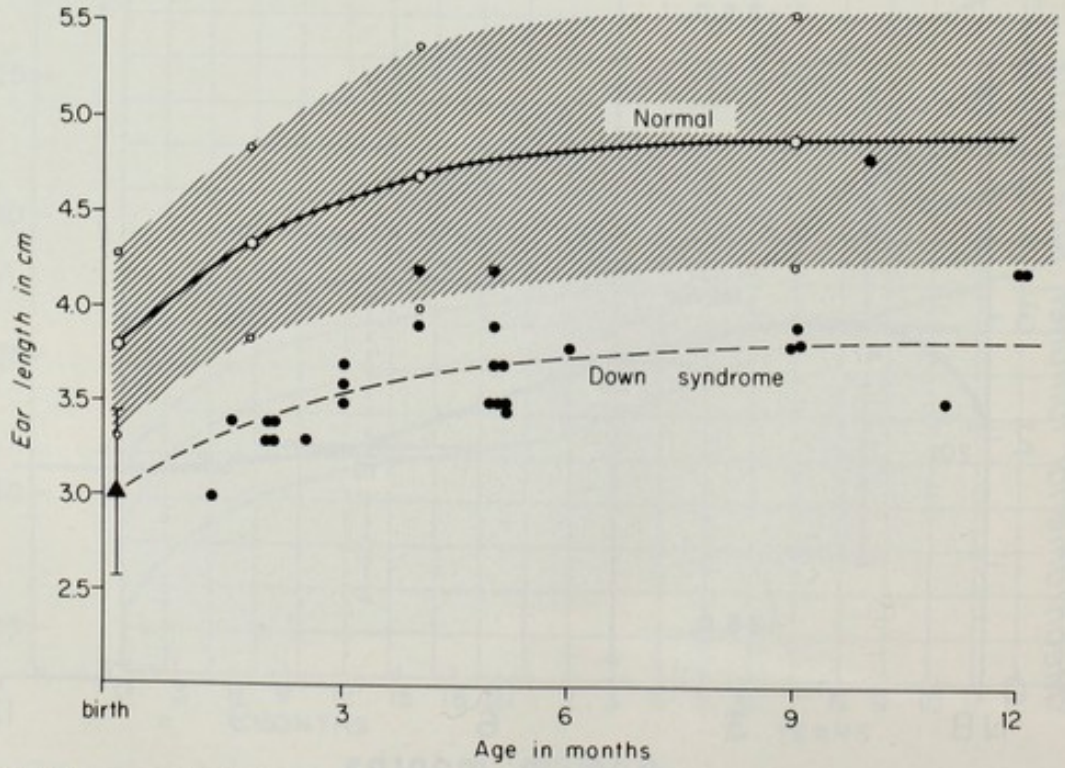


Mean anterior fontanel measurement (length plus width divided by two) during the first year. The numbers below the mean line indicate the number of normal infants measured at each age. Note: The posterior fontanel was fingertip size or smaller in dimension in 97 per cent of newborn infants. (From Popich, G., and Smith, D. W.: J. Pediatr., *80*:749, 1972.)

EAR LENGTH

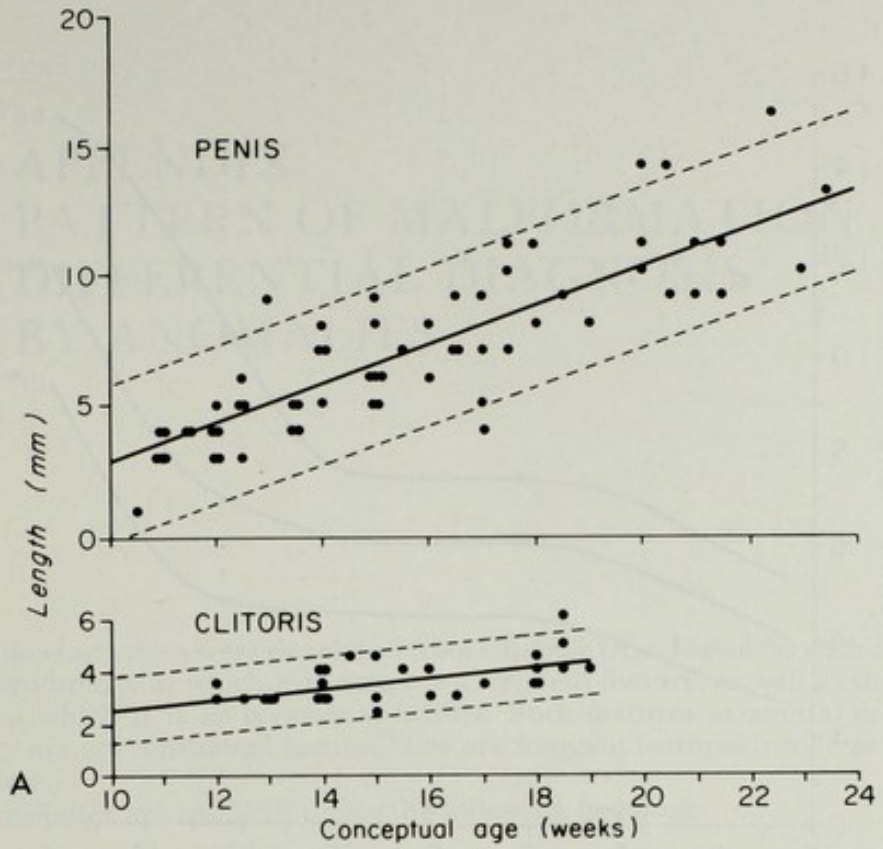


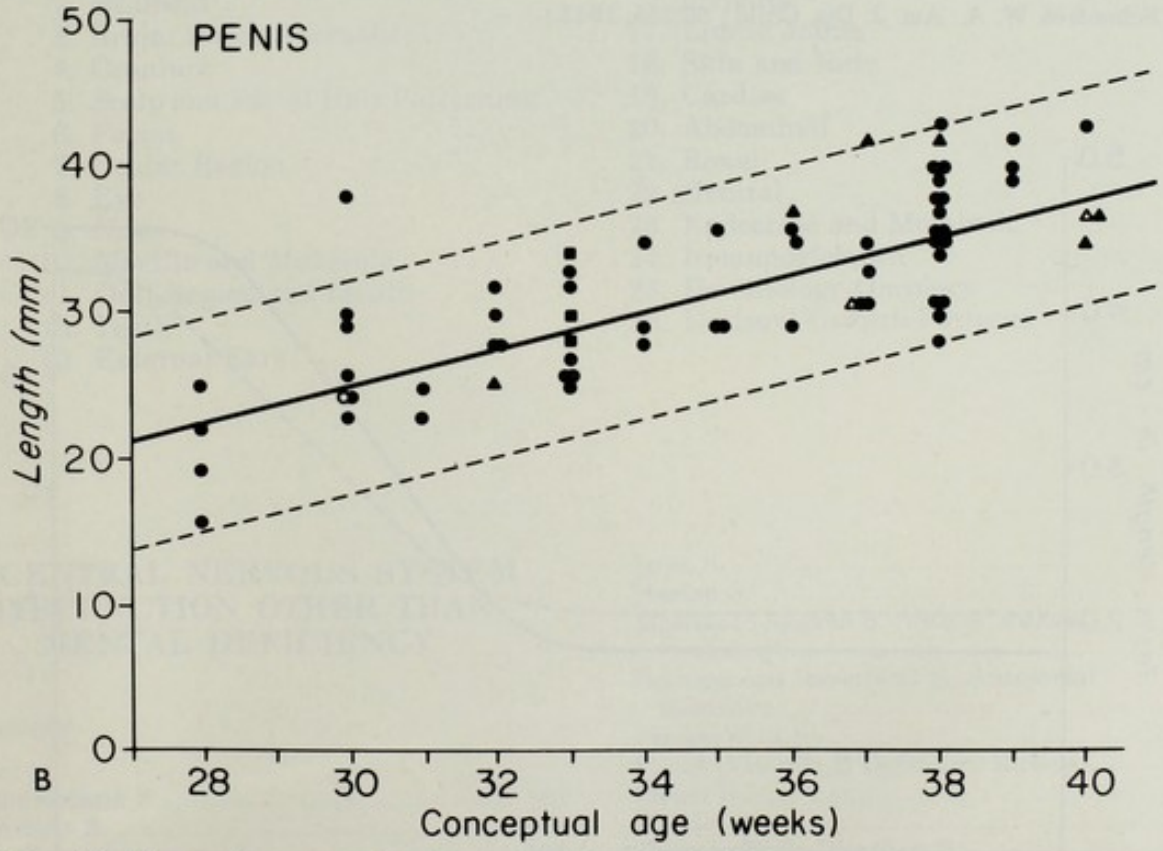
Maximum ear length. (From Feingold, M., and Bossert, W. H.: Birth Defects, *10*:No. 13, 1974.)



Ear length in normals during the first year, showing mean and two standard deviations in hatched area as contrasted to ear length in the Down syndrome, showing mean and two standard deviations for 26 affected newborns and individual values (black dots) during first year. (From Aase, J. M., et al.: J. Pediatr., *82*:845, 1973.)

PENILE LENGTH

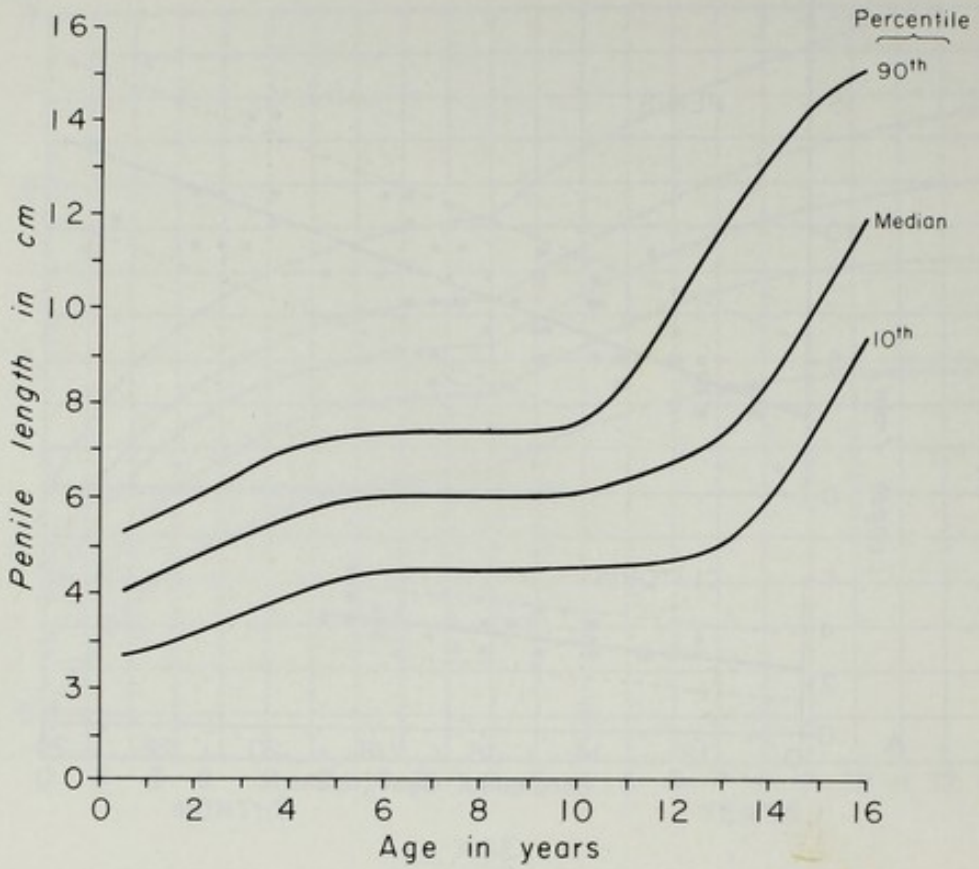




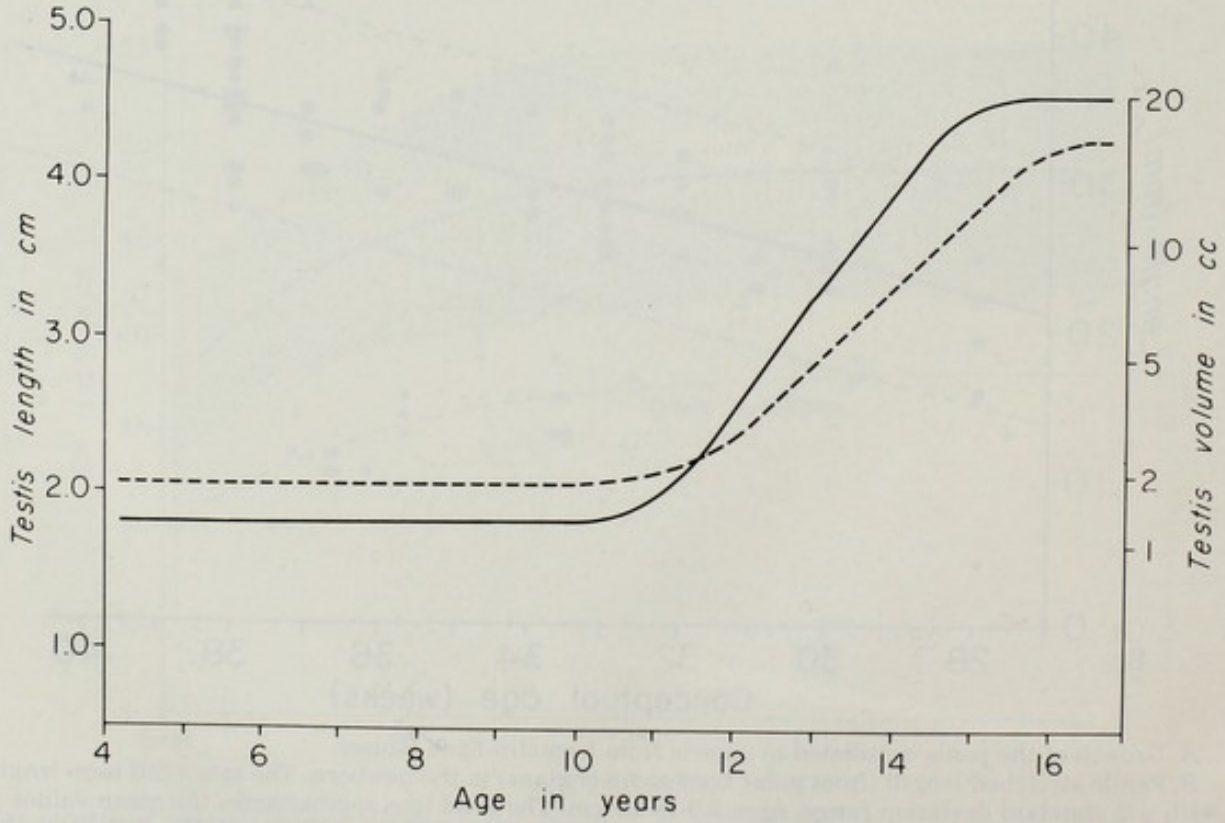
A, Growth of the penis contrasted to clitoris from formalin-fixed fetuses.

B, Penile stretched length (from pubic bone to tip of glans) in the newborn. The mean full term length is 3.5 cm with a 2 standard deviation range, from 2.8 to 4.2 cm. The solid line approximates the mean values and the broken lines the two standard deviation values. (From Feldman, K. W., and Smith, D. W.: J. Pediatr., in press, 1975.)

PENILE AND TESTICULAR GROWTH



Penile growth in stretched length from the pubic ramus to the tip of the glans; from infancy into adolescence. (From Schonfeld, W. A.: Am. J. Dis. Child., *65*:535, 1943.)



Testicular growth in length, adapted from normal standards of testicular volume. (Solid line from data of A. Prader, Zurich; broken line from data of Laron, A., and Zilka, E.: J. Clin. Endocrinol. Metab., *29*:1409, 1969.)

APPENDIX: PATTERN OF MALFORMATION DIFFERENTIAL DIAGNOSIS BY ANOMALIES

The following tables were developed from Chapter One. Listed for each anomaly are the syndromes in which this defect is a frequent feature, as well as those syndromes in which it is an occasional feature. Such features as mental or growth deficiency are not considered because they are frequent features in a large number of disorders.

The anomalies are set forth under the following headings:

1. Central Nervous System Dysfunction other than Mental Deficiency
2. Deafness
3. Brain: Major Anomalies
4. Cranium
5. Scalp and Facial Hair Patterning
6. Facies
7. Ocular Region
8. Eye
9. Nose
10. Maxilla and Mandible
11. Oral Region and Mouth
12. Teeth
13. External Ears
14. Neck, Thorax, and Vertebrae
15. Limbs
16. Limbs: Nails, Creases, Dermatoglyphics
17. Limbs: Joints
18. Skin and Hair
19. Cardiac
20. Abdominal
21. Renal
22. Genital
23. Endocrine and Metabolic
24. Immunoglobulin
25. Hematology-Oncology
26. Unusual Growth Patterns

1. CENTRAL NERVOUS SYSTEM DYSFUNCTION OTHER THAN MENTAL DEFICIENCY

Hypotonicity

Frequent in

Achondroplasia S. 188
Coffin-Siris S. 348
Cohen S. 108
Down S. 6
Fetal Warfarin S. 342
Generalized Gangliosidosis S. 260
Langer-Giedion S. 158
Lowe S. 112
Marfan S. 276
Marinesco-Sjögren S. (with or without weakness) 101
Osteogenesis Imperfecta S., Autosomal Recessive 288
Prader-Willi S. 106
Pseudo-Vitamin D Deficiency Rickets 216
Rieger S. 352
Stickler S. 154
Thanatophoric Dwarfism S. 180
XXXXY S. 40
Zellweger S. 110
4p – S. 22
18q – S. 30

Occasional in
- Aminopterin S. 340
- Blepharophimosis S. 122
- Cri-du-Chat S. 24
- Fabry S. 360
- Steinert Myotonic Dystrophy S. 114
- Trisomy 13 S. 14
- Williams S. 54

Hypertonicity

Frequent in
- De Lange S. 56
- Hunter S. 270
- Menkes S. 104
- Sjögren-Larsson S. 100
- Smith-Lemli-Opitz S. 82
- Trisomy 18 S. 10
- Weaver S. 90
- 18p−S. 28
- 21q−S. 32

Occasional in
- Incontinentia Pigmenti S. 298
- Sturge-Weber Anomalad 294
- Trisomy 13 S. 14
- X-Linked Hydrocephalus S. 98

Ataxia

Frequent in
- Ataxia-Telangiectasia S. (onset one to five years) 102
- Cockayne S. 80
- De Sanctis–Cacchione S. 66
- Marinesco-Sjögren S. 101

Seizures

Frequent in
- De Sanctis–Cacchione S. 66
- DiGeorge Anomalad 374
- Generalized Gangliosidosis S. 260
- Linear Sebaceous Nevus Anomalad 296
- Menkes S. 104
- Neurocutaneous Melanosis Anomalad 295
- Pseudo-Vitamin D Deficiency Rickets 216
- Sturge-Weber Anomalad 294
- Trisomy 13 S. 14
- Tuberous Sclerosis S. 300
- Zellweger S. 110
- 4p−S. 22

Occasional in
- Chediak-Higashi S. 363
- De Lange S. 56
- Down S. 6
- Fabry S. 360
- Fetal Warfarin S. 342
- Incontinentia Pigmenti S. 298
- Klippel-Trenaunay-Weber S. 306
- Lowe S. 112
- Neurofibromatosis S. 302
- Oral-Facial-Digital S. 144
- Osler Hemorrhagic Telangiectasia S. 313
- Prader-Willi S. 106
- Riley-Day S. 361
- Robinow S. 86
- Rubinstein-Taybi S. 58
- Sjögren-Larsson S. 100
- Smith-Lemli-Opitz S. 82
- Sotos S. 88
- 21q−S. 32

2. DEAFNESS

Frequent in
- Cockayne S. 80
- Facio-Auriculo-Vertebral Anomalad 136
- Gorlin Fronto-Metaphyseal Dysplasia S. 222
- Hunter S. 270
- Hurler S. 264
- Mohr S. 146
- Morquio S. 272
- Multiple Lentigines S. 318
- Multiple Synostosis S. 244
- Oto-Palato-Digital S. 150
- Robinson Nail Dystrophy-Deafness S. 328
- Rubella S. 338
- Stickler S. 154
- Treacher Collins S. 134
- Trisomy 13 S. 14
- Waardenburg S. 124
- 18q−S. 30

Occasional in
- Camurati-Engelmann S. 282
- Cleidocranial Dysostosis S. 230
- Crouzon S. 234
- Diastrophic Dwarfism S. 202
- EEC S. 162
- Fanconi Pancytopenia S. 174
- Fetal Trimethadione S. 344
- Frontonasal Dysplasia Anomalad 128
- Langer-Giedion S. 158
- Laurence-Moon-Biedl S. 350
- Noonan S. 50
- Oculodentodigital S. 148
- Osteogenesis Imperfecta Tarda S. 286
- Progeria S. 76
- Saethre-Chotzen S. 236
- Scheie S. 275
- Trisomy 8 S. 18
- Turner S. (partial) 46
- Weill-Marchesani S. 257

3. BRAIN: MAJOR ANOMALIES

Encephalocele

Frequent in
- Meckel-Gruber S. 96

Occasional in
- Amniotic Band Anomalads 166
- Facio-Auriculo-Vertebral Anomalad 136
- Roberts S. 164

Hydrocephalus

Frequent in
- Albers-Schönberg S. 226
- X-Linked Hydrocephalus S. 98

Occasional in
- Achondroplasia S. 188
- Acrodysostosis S. 253
- Apert S. 242
- Basal Cell Nevus S. 316
- Hurler S. 264
- Incontinentia Pigmenti S. 298
- Linear Sebaceous Nevus Anomalad 296
- Meckel-Gruber S. 96
- Oral-Facial-Digital S. 144

Osteogenesis Imperfecta S., Autosomal Recessive ... 288
Riley-Day S. ... 361
Roberts S. ... 164
Thanatophoric Dwarfism S. ... 180
Triploidy S. ... 20
Trisomy 13 S. ... 14
Trisomy 18 S. ... 10

Microcephaly

Frequent in

Aminopterin S. ... 340
Bloom S. ... 64
Coffin-Siris S. ... 348
Cri-du-Chat S. ... 24
De Lange S. ... 56
De Sanctis-Cacchione S. ... 66
Dubowitz S. ... 62
Fetal Alcohol S. ... 336
Johanson-Blizzard S. ... 68
Langer-Giedion S. ... 158
Meckel-Gruber S. ... 96
Roberts S. ... 164
Rubella S. ... 338
Seckel S. ... 70
Smith-Lemli-Opitz S. ... 82
Thanatophoric Dwarfism S. ... 180
Trisomy 13 S. ... 14
Trisomy 18 S. ... 10
Williams S. ... 54
4p−S. ... 22
13q−S. ... 26
18p−S. ... 28
18q−S. ... 30

Occasional in

Aniridia-Wilms' Tumor Association ... 390
Fanconi Pancytopenia S. ... 174
Fetal Hydantoin S. ... 346
Goltz S. ... 320
Incontinentia Pigmenti S. ... 298
Klippel-Trenaunay-Weber S. ... 306
Riley-Day S. ... 361
Steinert Myotonic Dystrophy S. ... 114
XXXXY S. ... 40

Macrocephaly

Frequent in

Achondroplasia S. ... 188
Albers-Schönberg S. ... 226
Hunter S. ... 270
Hurler S. ... 264
Hyperphosphatasia-Osteoectasia S. ... 220
Marshall S. ... 92
Robinow S. ... 86
Sotos S. ... 88
Weaver S. ... 90

Occasional in

Beckwith-Wiedemann S. ... 94
Camptomelic Dwarfism S. ... 184
Generalized Gangliosidosis S. ... 260
Klippel-Trenaunay-Weber S. ... 306
Maroteaux-Lamy Mucopolysaccharidosis S. ... 268
Morquio S. ... 272
Neurofibromatosis S. ... 302
Sturge-Weber Anomalad ... 294

4. CRANIUM

Craniosynostosis

Frequent in

Acrodysostosis S. ... 253
Apert S. ... 242
Carpenter S. ... 240
Crouzon S. ... 234
Fetal Trimethadione S. ... 344
Pfeiffer S. ... 238
Saethre-Chotzen S. ... 236

Occasional in

Aminopterin S. ... 340
Conradi-Hünermann S. ... 211
Fetal Hydantoin S. ... 346
Hypophosphatasia S. ... 218
Lowe S. ... 112
Meckel-Gruber S. ... 96
Tricho-Dento-Osseous S. ... 330
Williams S. ... 54
X-Linked Hypophosphatemic Rickets ... 214

Occiput, Flat or Prominent

Frequent in

Apert S. (flat) ... 242
Carpenter S. (flat) ... 240
Down S. (flat) ... 6
Opitz-Frias S. (prominent) ... 84
Oto-Palato-Digital S. (prominent) ... 150
Trisomy 18 S. (prominent) ... 10
Weaver S. (prominent) ... 90
Zellweger S. (flat) ... 110

Occasional in

XXXXY S. (flat) ... 40

Delayed Closure of Fontanels

Frequent in

Aase S. ... 177
Aminopterin S. ... 340
Apert S. ... 242
Athyrotic Hypothyroidism Anomalad ... 372
Cleidocranial Dysostosis S. ... 230
Down S. ... 6
Fetal Hydantoin S. ... 346
Hallermann-Streiff S. ... 72
Hypophosphatasia S. ... 218
Kenny S. ... 217
Maroteaux-Lamy Pyknodysostosis S. ... 228
Osteogenesis Imperfecta S., Autosomal Recessive ... 288
Progeria S. ... 76
Pseudo-Vitamin D Deficiency Rickets ... 216
Robinow S. ... 86
Stanesco Dysostosis S. ... 232
Thanatophoric Dwarfism S. ... 180
Triploidy S. ... 20
Trisomy 13 S. ... 14
Trisomy 18 S. ... 10
Zellweger S. ... 110

Occasional in

Conradi-Hünermann S. ... 211
Cutis Laxa-Growth Deficiency S. ... 358
Oto-Palato-Digital S. ... 150

Rubinstein-Taybi S. 58
VATER Association 388

Frontal Bossing or Prominent Central Forehead

Frequent in
Albers-Schönberg S. 226
Basal Cell Nevus S. 316
Crouzon S. 234
Fetal Trimethadione S. 344
Generalized-Gangliosidosis S. 260
Hallermann-Streiff S. 72
Hurler S. 264
Hyperphosphatasia-Osteoectasia S. 220
Leroy I-Cell S. 262
Marshall S. 92
Oto-Palato-Digital S. 150
Pfeiffer S. 238
Robinow S. 86
Rubinstein-Taybi S. 58
Russell-Silver S. 60
Tricho-Dento-Osseous S. 330
Trisomy 8 S. 18

Occasional in
Hypochondroplasia S. 190
Oral-Facial-Digital S. 144

5. SCALP AND FACIAL HAIR PATTERNING

Anterior Upsweep, Scalp

Frequent in
Aminopterin S. 340
Rubinstein-Taybi S. 58
Trisomy 13 S. 14

Occasional in
Prader-Willi S. 106

Posterior Midline Scalp Defects

Frequent in
Johanson-Blizzard S. 68
Trisomy 13 S. 14
4p–S. 22

6. FACIES

"Flat" Facies

Frequent in
Achondroplasia S. 188
Apert S. 242
Camptomelic Dwarfism S. 184
Carpenter S. 240
Conradi-Hünermann S. 211
Down S. 6
Larsen S. 156
Rhizomelic Chondrodysplasia Punctata S. 212
Schwartz S. 116
Spondyloepiphyseal Dysplasia Congenita S. 194
Stickler S. 154
XXXXX S. 44
XXXXY S. 40
Zellweger S. 110

Occasional in
Basal Cell Nevus S. 316
Cleidocranial Dysostosis S. 230
Crouzon S. 234
Leroy I-Cell S. 262
Marshall S. 92
Trisomy 13 S. 14
Waardenburg S. 124
4p–S. 22

"Round" Facies

Frequent in
Aarskog S. 52
Albright Hereditary Osteodystrophy S. 254
Cri-du-Chat S. 24
Prader-Willi S. 106
18p–S. 28

Occasional in
Basal Cell Nevus S. 316
Cleidocranial Dysostosis S. 230
Down S. 6
Laurence-Moon-Biedl S. 350
XXXXX S. 44
XXXXY S. 40
Zellweger S. 110

Broad Facies

Frequent in
Apert S. 242
Basal Cell Nevus S. 316
Carpenter S. 240
Crouzon S. 234

Occasional in
Cleidocranial Dysostosis S. 230
Laurence-Moon-Biedl S. 350
Prader-Willi S. 106
Sotos S. 88
XXXXY S. 40

"Triangular" Facies

Frequent in
Russell-Silver S. 60
Turner S. 46

Occasional in
Facio-Auriculo-Vertebral Anomalad 136
Hallermann-Streiff S. 72
Treacher Collins S. 134

Mask-Like Facies

Frequent in
Facio-Auriculo-Vertebral Anomalad 136
Freeman-Sheldon S. 113
Moebius Anomalad 118
Schwartz S. 116
Steinert Myotonic Dystrophy S. 114

"Coarse" Facies

Frequent in
Athyrotic Hypothyroidism Anomalad 372
Coffin-Lowry S. 152
Coffin-Siris S. 348
Geleophysic Dwarfism S. 198
Generalized Gangliosidosis S. 260
Gorlin Fronto-Metaphyseal Dysplasia S. 222

Hunter S. 270
Hurler S. 264
Leroy I-Cell S. 262
Maroteaux-Lamy Mucopolysaccharidosis S. 268
Morquio S. 272
Multiple Neuroma S. 314
Pachydermoperiostosis S. 334
Pseudo-Hurler Polydystrophy S. 266
Sanfilippo S. 274
Scheie S. 275
Sotos S. 88
Williams S. 54

7. OCULAR REGION

Hypotelorism

Frequent in

Holoprosencephaly Anomalad 366
Trisomy 13 S. 14

Occasional in

Coffin-Siris S. 348
Meckel-Gruber S. 96
Williams S. 54

Hypertelorism

Frequent in

Aarskog S. 52
Acrodysostosis S. 253
Aminopterin S. 340
Apert S. 242
Cleft Lip and Palate Anomalad 132
Coffin-Lowry S. 152
DiGeorge Anomalad 374
Fetal Hydantoin S. 346
Frontonasal Dysplasia Anomalad 128
Larsen S. 156
Multiple Lentigines S. 318
Noonan S. 50
Opitz S. 126
Opitz-Frias S. 84
Oto-Palato-Digital S. 150
Pfeiffer S. 238
Pyle S. 225
Roberts S. 164
Robinow S. 86
Saethre-Chotzen S. 236
Sotos S. 88
Trisomy 8 S. 18
Weaver S. 90
XXXX S. 42
4p−S. 22
13q−S. 26

Occasional in

Basal Cell Nevus S. 316
Camptomelic Dwarfism S. 184
Cleidocranial Dysostosis S. 230
Coloboma of Iris-Anal Atresia S. 34
Conradi-Hünermann S. 211
Cri-du-Chat S. 24
Crouzon S. 234
Cryptophthalmos S. 121
Holt-Oram S. 172
Hurler S. 264
Meckel-Gruber S. 96
Noonan S. 50
Sjögren-Larsson S. 100
Triploidy S. 20
XXXXX S. 44
XXXXY S. 40
18p−S. 28
18q−S. 30

Short Palpebral Fissure

Frequent in

Dubowitz S. 62
Fetal Alcohol S. 336
Trisomy 18 S. 10
Williams S. 54

Lateral Displacement of Inner Canthi (giving rise to short palpebral fissures)

Frequent in

Blepharophimosis S. 122
Carpenter S. 240
Frontonasal Dysplasia Anomalad 128
Mohr S. 146
Oral-Facial-Digital S. 144
Waardenburg S. 124

Occasional in

Basal Cell Nevus S. 316
Oculodentodigital S. 148

Inner Epicanthal Folds

Frequent in

Blepharophimosis S. 122
Coloboma of Iris-Anal Atresia S. 34
Cri-du-Chat S. 24
Down S. 6
Fetal Trimethadione S. 344
Freeman-Sheldon S. 113
Hurler S. 264
Leroy I-Cell S. 262
Noonan S. 50
Rubinstein-Taybi S. 58
Smith-Lemli-Opitz S. 82
Stickler S. 154
Turner S. 46
Williams S. 54
XXXX S. 42
XXXXX S. 44
XXXXY S. 40
Zellweger S. 110
4p−S. 22
13q−S. 26
18p−S. 28

Occasional in

Acrodysostosis S. 253
Aminopterin S. 340
Basal Cell Nevus S. 316
Distichiasis-Lymphedema S. 359
Ehlers-Danlos S. 284
Oculodentodigital S. 148
Robinow S. 86
Trisomy 18 S. 10
18q−S. 30

Slanted Palpebral Fissures

Frequent in

Aarskog S. (down) 52
Apert S. (down) 242
Coffin-Lowry S. (down) 152

Cohen S. (down) 108
Coloboma of Iris-Anal Atresia S. (down) 34
Conradi-Hünermann S. (down) 211
Cri-du-Chat S. (up or down) 24
DiGeorge Anomalad (down) 374
Down S. (up) 6
Femoral Hypoplasia-Unusual Facies S. (down) 170
Leri Pleonosteosis (up) 349
Opitz-Frias S. 84
Pfeiffer S. (up) 238
Rhizomelic Chondrodysplasia Punctata S. (up) 212
Rubinstein-Taybi S. (down) 58
Saethre-Chotzen S. (down) 236
Sotos S. (down) 88
Treacher Collins S. (down) 134
XXXXX S. (up) 44
XXXXY S. (up) 40

Occasional in
Fetal Hydantoin S. (up) 346
Hallermann-Streiff S. (down) 72
Prader-Willi S. (up) 106
Trisomy 13 S. (up) 14
Trisomy 18 S. (up) 10
XXXXY S. (up) 40
18q−S. (up) 30

Shallow Orbital Ridges

Frequent in
Aminopterin S. 340
Apert S. 242
Carpenter S. 240
Crouzon S. 234
Dubowitz S. 62
Marshall S. 92
Osteogenesis Imperfecta S., Autosomal Recessive 288
Roberts S. 164
Stanesco Dysostosis S. 232
Trisomy 18 S. 10
Zellweger S. 110

Occasional in
Trisomy 13 S. 14

Prominent Supraorbital Ridges

Frequent in
Gorlin Fronto-Metaphyseal Dysplasia S. 222
Oto-Palato-Digital S. 150
Pyle Metaphyseal Dysplasia S. 225

Prominent Eyes

Frequent in
Aminopterin S. 340
Apert S. 242
Beckwith-Wiedemann S. 94
Jansen S. 208
Leprechaunism S. 356
Pyle S. 225
Roberts S. 164

Periorbital Fullness of Subcutaneous Tissues

Frequent in
Athyrotic Hypothyroidism Anomalad 372
Williams S. 54

Eyebrows Extending to Midline

Frequent in
De Lange S. 56
Fetal Trimethadione S. 344
Waardenburg S. 124

Occasional in
Basal Cell Nevus S. 316
Trisomy 13 S. 14
4p−S. 22

Unusual Flare of Medial Eyebrow

Frequent in
Waardenburg S. 124
Williams S. 54

Ptosis of Eyelid

Frequent in
Aarskog S. 52
Blepharophimosis S. 122
Dubowitz S. 62
Fetal Trimethadione S. 344
Freeman-Sheldon S. 113
Moebius Anomalad 118
Pachydermoperiostosis S. 334
Schwartz S. 116
Saethre-Chotzen S. 236
Smith-Lemli-Opitz S. 82
Steinert Myotonic Dystrophy S. 114
13q−S. 26
18p−S. 28

Occasional in
Coffin-Siris S. 348
Fanconi Pancytopenia S. 174
Fetal Alcohol S. 336
Fetal Hydantoin S. 346
Noonan S. 50
Rubinstein-Taybi S. 58
Trisomy 18 S. 10
Turner S. 46

Strabismus

Frequent in
Apert S. 242
Clouston S. 329
Cohen S. 108
Cri-du-Chat S. 24
Fetal Trimethadione S. 344
Freeman-Sheldon S. 113
Goltz S. 320
Incontinentia Pigmenti S. 298
Mietens S. 147
Noonan S. 50
Prader-Willi S. 106
Rubella S. 338
Rubinstein-Taybi S. 58
Smith-Lemli-Opitz S. 82
Trisomy 8 S. 18
Trisomy 18 S. 10
Turner S. 46
Williams S. 54
XXXXY S. 40
4p−S. 22

Occasional in
Basal Cell Nevus S. 316

Blepharophimosis S. 122
De Lange S. 56
Down S. 6
Facio-Auriculo-Vertebral Anomalad 136
Fanconi Pancytopenia S. 174
Femoral Hypoplasia-Unusual Facies S. 170
Fetal Alcohol S. 336
Fetal Hydantoin S. 346
Hallermann-Streiff S. 72
Johanson-Blizzard S. 68
Laurence-Moon-Biedl S. 350
Marinesco-Sjögren S. 101
Radial Aplasia-Thrombocytopenia S. 176
Saethre-Chotzen S. 236
Seckel S. 70
Sotos S. 88
18p−S. 28

Nystagmus

Frequent in

Chediak-Higashi S. 363
Marinesco-Sjögren S. 101
Septo-Optic Dysplasia Anomalad 370
18q−S. 30

Occasional in

Blepharophimosis S. 122
Cockayne S. 80
Down S. 6
Fanconi Pancytopenia S. 174
Hallermann-Streiff S. 72
Laurence-Moon-Biedl S. 350
Zellweger S. 110

8. EYE

Myopia

Frequent in

Cohen S. 108
Homocystinuria S. 280
Kenny S. 217
Marfan S. 276
Marshall S. 92
Noonan S. 50
Pseudoxanthoma Elasticum S. 292
Schwartz S. 116
Spondyloepiphyseal Dysplasia Congenita S. 194
Stickler S. 154
Weill-Marchesani S. 257

Occasional in

Cri-du-Chat S. 24
De Lange S. 56
Ehlers-Danlos S. 284
Fetal Trimethadione S. 344
Scheie S. 275
XXXXY S. 40

Blue Sclerae

Frequent in

Hyperphosphatasia-Osteoectasia S. 220
Marshall S. 92
Osteogenesis Imperfecta S., Autosomal Recessive 288
Roberts S. 164
Russell-Silver S. 60

Occasional in

Ehlers-Danlos S. 284
Hallermann-Streiff S. 72
Incontinentia Pigmenti S. 298
Marfan S. 276
Trisomy 18 S. 10

Microphthalmos

Frequent in

Frontonasal Dysplasia Anomalad 128
Goltz S. 320
Hallermann-Streiff S. 72
Meckel-Gruber S. 96
Oculodentodigital S. 148
Rubella S. 338
Triploidy S. 20
Trisomy 13 S. 14
4p−S. 22
13q−S. 26

Occasional in

Cohen S. 108
Facio-Auriculo-Vertebral Anomalad 136
Fanconi Pancytopenia S. 174
Trisomy 18 S. 10
18q−S. 30

Colobomata of Iris

Frequent in

Coloboma of Iris-Anal Atresia S. 34
Goltz S. 320
Rieger S. 352
Triploidy S. 20
Trisomy 13 S. 14
4p−S. 22
13q−S. 26

Occasional in

Basal Cell Nevus S. 316
Cohen S. 108
Fetal Hydantoin S. 346
Facio-Auriculo-Vertebral Anomalad 136
Linear Sebaceous Nevus Anomalad 296
Marfan S. 276
Meckel-Gruber S. 96
Rubinstein-Taybi S. 58
Sturge-Weber Anomalad 294
Trisomy 18 S. 10
XXXXX S. 44

Iris, Unusual Patterning or Coloration

Frequent in

Down S. (Brushfield spots) 6
EEC S. (blue) 162
Williams S. (stellate) 54

Glaucoma

Frequent in

Stickler S. 154
Weill-Marchesani S. 257

Occasional in

Basal Cell Nevus S. 316
Ehlers-Danlos S. 284
Facio-Auriculo-Vertebral Anomalad 136
Hallermann-Streiff S. 72
Homocystinuria S. 280
Klippel-Trenaunay-Weber S. 306

Lowe S. ... 112
Marfan S. ... 276
Neurofibromatosis S. ... 302
Oculodentodigital S. ... 148
Rieger S. ... 352
Rubella S. ... 338
Scheie S. ... 275
Sturge-Weber Anomalad ... 294
Treacher Collins S. ... 134
Zellweger S. ... 110

Keratoconus, Microcornea

Frequent in

Noonan S. ... 50
Oculodentodigital S. ... 148

Occasional in

De Lange S. ... 56
Down. S. ... 6
Ehlers-Danlos S. ... 284
Nail-Patella S. ... 248
Osteogenesis Imperfecta S., Autosomal Recessive ... 288
Rieger S. ... 352

Corneal Opacity

Frequent in

Fabry S. ... 360
Hurler S. ... 264
Maroteaux-Lamy Mucopolysaccharidosis S. ... 268
Mietens S. ... 147
Morquio S. ... 272
Pseudo-Hurler Polydystrophy S. ... 266
Rubella S. ... 338
Scheie S. ... 275

Occasional in

Berardinelli S. ... 357
Chediak-Higashi S. ... 363
Cockayne S. ... 80
Linear Sebaceous Nevus Anomalad ... 296
Neurofibromatosis S. ... 302
Osteogenesis Imperfecta S. Autosomal Recessive ... 288
Pachyonychia Congenita S. ... 332
Rieger S. ... 352
Roberts S. ... 164
Trisomy 18 S. ... 10
18q−S. ... 30

Cataract, Lenticular Opacities

Frequent in

Aniridia-Wilms' Tumor Association ... 390
Conradi-Hünermann S. ... 211
Hallermann-Streiff S. ... 72
Lowe S. ... 112
Marinesco-Sjögren S. ... 101
Rhizomelic Chondrodysplasia Punctata S. ... 212
Rothmund-Thomson S. ... 74
Rubella S. ... 338
Steinert Myotonic Dystrophic S. ... 114
Stickler S. ... 154
Werner S. ... 78

Occasional in

Albright Hereditary Osteodystrophy S. ... 254
Basal Cell Nevus S. ... 316
Clouston S. ... 329
Cockayne S. ... 80
Conradi-Hünermann S. ... 211
Down S. ... 6
Homocystinuria S. ... 280
Incontinentia Pigmenti S. ... 298
Nail-Patella S. ... 248
Pachyonychia Congenita S. ... 332
Progeria S. ... 76
Roberts S. ... 164
Rubinstein-Taybi S. ... 58
Smith-Lemli-Opitz S. ... 82
Trisomy 18 S. ... 10
Zellweger S. ... 110
18p−S. ... 28
18q−S. ... 30
21q−S. ... 32

Lens Dislocation

Frequent in

Homocystinuria S. ... 280
Marfan S. ... 276
Weill-Marchesani S. ... 257

Occasional in

Ehlers-Danlos S. ... 284
Rieger S. ... 352

Retinal Pigmentation

Frequent in

Chediak-Higashi S. ... 363
Cockayne S. ... 80
Cohen S. ... 108
Hurler S. ... 264
Laurence-Moon-Biedl S. ... 350
Rubella S. ... 338
Werner S. ... 78

Occasional in

Hallermann-Streiff S. ... 72
Hunter S. ... 270
Sjögren-Larsson S. ... 100

9. NOSE

Low Nasal Bridge

Frequent in

Achondrogenesis S. ... 178
Achondroplasia S. ... 188
Acrodysostosis S. ... 253
Albright Hereditary Osteodystrophy S. ... 254
Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. ... 326
Blepharophimosis S. ... 122
Camptomelic Dwarfism S. ... 184
Carpenter S. ... 240
Cleidocranial Dysostosis S. ... 230
Conradi-Hünermann S. ... 211
Down S. ... 6
Fetal Hydantoin S. ... 346
Fetal Trimethadione S. ... 344
Fetal Warfarin S. ... 342
Generalized Gangliosidosis S. ... 260
Hurler S. ... 264
Hypohidrotic Ectodermal Dysplasia S. ... 324
Larsen S. ... 156
Maroteaux-Lamy Mucopolysaccharidosis S. ... 268
Marshall S. ... 92
Mohr S. ... 146

Osteogenesis Imperfecta Syndromes..... 286, 288
Pfeiffer S. 238
Rapp-Hodgkin Ectodermal Dysplasia S..... 327
Rhizomelic Chondrodysplasia Punctata S..... 212
Thanatophoric Dwarfism S..... 180
Williams S..... 54
XXXXX S..... 44
XXXXY S..... 40
Zellweger S..... 110
18p– S. 28
18q– S. 30

Occasional in
Ehlers-Danlos S..... 284
Fraser S. 121
Triploidy S..... 20

Broad Nasal Bridge

Frequent in
Basal Cell Nevus S. 316
Fetal Hydantoin S. 346
Fetal Trimethadione S. 344
Gorlin Fronto-Metaphyseal Dysplasia S..... 222
Trisomy 8 S. 18

Small or Short Nose, with or without Anteverted Nostrils

Frequent in
Aarskog S..... 52
Acrodysostosis S. 253
Apert S. 242
De Lange S..... 56
Femoral Hypoplasia-Unusual Facies S. 170
Fetal Trimethadione S. 344
Geleophysic Dwarfism S. 198
Hallermann-Streiff S..... 72
Leroy I-Cell S..... 262
Marshall S..... 92
Osteogenesis Imperfecta S., Autosomal Recessive..... 288
Oto-Palato-Digital S..... 150
Pfeiffer S. 238
Robinow S. 86
Trisomy 18 S..... 10
Williams S..... 54

Occasional in
Down S. 6
Rothmund-Thomson S. 74
Treacher Collins S. 134
Trisomy 13 S..... 14
Waardenburg S. 124
XXXXY S..... 40

Hypoplasia of Nares

Frequent in
Cleft Lip and Palate Anomalad..... 132
Cryptophthalmos S. 121
Femoral Hypoplasia-Unusual Facies S. 170
Fetal Warfarin S. 342
Freeman-Sheldon S..... 113
Hallermann-Streiff S..... 72
Johanson-Blizzard S..... 68
Mietens S. 147
Multiple Synostosis S..... 244
Oculodentodigital S..... 148
Oral-Facial-Digital S..... 144
Rapp-Hodgkin S. 327
Roberts S..... 164
Schwartz S..... 116

Occasional in
Waardenburg S. 124

Prominent Nose (Relative)

Frequent in
Coffin-Lowry S. 152
Langer-Giedion S..... 158
Maroteaux-Lamy Pyknodysostosis S..... 228
Rubinstein-Taybi S. 58
Seckel S. 70
Tricho-Rhino-Phalangeal S. 160
13q– S. 26
21q– S. 32

Occasional in
Bloom S..... 64
Stanesco S. 232
Trisomy 13 S..... 14
14p– S. 22

10. MAXILLA AND MANDIBLE

Malar Hypoplasia

Frequent in
Bloom S..... 64
Conradi-Hünermann S. 211
EEC S..... 162
Facio-Auriculo-Vertebral Anomalad..... 136
Hallermann-Streiff S..... 72
Oto-Palato-Digital S..... 150
Maroteaux-Lamy Pyknodysostosis S..... 228
Seckel S. 70
Spondyloepiphyseal Dysplasia Congenita S..... 194
Stanesco Dysostosis S..... 232
Treacher Collins S. 134
21q– S. 32

Occasional in
Cockayne S..... 80
Oral-Facial-Digital S..... 144
Trisomy 13 S..... 14
Trisomy 18 S..... 10
Williams S..... 54

Maxillary Hypoplasia, often with Narrow or High Arched Palate

Frequent in
Aarskog S..... 52
Achondroplasia S..... 188
Acrodysostosis S. 253
Apert S. 242
Bloom S..... 64
Cockayne S..... 80
Coffin-Lowry S. 152
Cohen S..... 108
Crouzon S..... 234
De Lange S..... 56
Facio-Auriculo-Vertebral Anomalad..... 136
Fetal Alcohol S..... 336
Fetal Trimethadione S. 344
Gorlin Fronto-Metaphyseal Dysplasia S..... 222
Hallermann-Streiff S..... 72
Leprechaunism S..... 356
Maroteaux-Lamy Pyknodysostosis S..... 228
Pfeiffer S. 238
Progeria S. 76
Rapp-Hodgkin Ectodermal Dysplasia S..... 327
Rubinstein-Taybi S. 58

Russell-Silver S. 60
Saethre-Chotzen S. 236
Seckel S. 70
Sotos S. 88
Stickler S. 154
Treacher Collins S. 134
Tricho-Rhino-Phalangeal S. 160
Trisomy 8 S. 18
XXXX S. 42
18q− S. 30

Occasional in
Aminopterin S. 340
Mietens S. 147
Oculodentodigital S. 148
Oral-Facial-Digital S. 144
Robinow S. 86
Weill-Marchesani S. 257
13q− S. 26

Micrognathia

Frequent in
Achondrogenesis Syndromes 178, 179
Aminopterin S. 340
Bloom S. 64
Camptomelic Dwarfism S. 184
Cerebro-Costo-Mandibular S. 354
Cohen S. 108
Cri-du-Chat S. 24
De Lange S. 56
Femoral Hypoplasia-Unusual Facies S. 170
Fetal Trimethadione S. 344
Facio-Auriculo-Vertebral Anomalad 136
Gorlin Fronto-Metaphyseal Dysplasia S. 222
Hajdu-Cheney S. 221
Hallermann-Streiff S. 72
Hypoglossia-Hypodactyly S. 142
Jansen Metaphyseal Chondrodysplasia S. 208
Langer-Giedion S. 158
Langer Mesomelic Dwarfism S. 252
Maroteaux-Lamy Pyknodysostosis S. 228
Marshall S. 92
Meckel-Gruber S. 96
Moebius Anomalad 118
Oral-Facial-Digital S. 144
Progeria S. 76
Roberts S. 164
Robin Anomalad 130
Russell-Silver S. 60
Seckel S. 70
Smith-Lemli-Opitz S. 82
Stickler S. 154
Treacher Collins S. 134
Tricho-Rhino-Phalangeal S. 160
Trisomy 8 S. 18
Trisomy 18 S. 10
Turner S. 46
Weaver S. 90
XXXX S. 42
Zellweger S. 110
4p− S. 22
13q− S. 26
18p− S. 28
21q− S. 32

Occasional in
Conradi-Hünermann S. 211
Contractural Arachnodactyly S. 278
Diastrophic Dwarfism S. 202
Noonan S. 50
Radial Aplasia-Thrombocytopenia S. 176
Rubinstein-Taybi S. 58
Triploidy S. 20
Trisomy 13 S. 14

Prognathism

Frequent in
Acrodysostosis S. 253
Basal Cell Nevus S. 316
Beckwith-Wiedemann S. 94
Scheie S. 275
Sotos S. 88
XXXXY S. 40

Cleft Lip with or without Cleft Palate

Frequent in
Amniotic Band Anomalads (disruptive) 166
Cleft Lip and Palate Anomalad 132
EEC S. 162
Fetal Hydantoin S. 346
Fetal Trimethadione S. 344
Mohr S. 146
Oral-Facial-Digital S. 144
Popliteal Web S. 140
Rapp-Hodgkin Ectodermal Dysplasia S. 327
Roberts S. 164
Trisomy 18 S. 10
Van der Woude S. 138
4p− S. 22

Occasional in
Aase S. 177
Cri-du-Chat S. 24
Facio-Auriculo-Vertebral Anomalad 136
Larsen S. 156
Meckel-Gruber S. 96
Oculodentodigital S. 148
Opitz S. 126
Triploidy S. 20
Trisomy 18 S. 10
Waardenburg S. 124

Abnormal Philtrum

Frequent in
Aarskog S. (broad) 52
Cohen S. (short) 108
DiGeorge Anomalad (short) 374
Femoral Hypoplasia-Unusual Facies S. (long) 170
Freeman-Sheldon S. (long) 113
Geleophysic Dwarfism S. (flattened) 198
Generalized Gangliosidosis S. (long) 260
Langer-Giedion S. (prominent and long) 158
Oral-Facial-Digital S. (short) 144
Robinow S. (long) 86
Tricho-Rhino-Phalangeal S. (prominent and long) 160
Trisomy 13 S. 14
Weaver S. (long) 90
Williams S. (long) 54
4p− S. (short) 22

Occasional in
Meckel-Gruber S. 96

Prominent Full Lips

Frequent in
Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. 326

Coffin-Siris S. 348
Geleophysic Dwarfism S. (upper) 198
Hunter S. 270
Hurler S. 264
Hypohidrotic Ectodermal Dysplasia S. 324
Leprechaunism S. 356
Scheie S. 275
Trisomy 8 S. 18
Williams S. 54

Occasional in
Fabry S. 360

Lower Lip Pits

Frequent in
Popliteal Web S. 140
Van der Woude S. 138

Occasional in
Oral-Facial-Digital S. 144

Downturning Corners of Mouth

Frequent in
De Lange S. 56
Russell-Silver S. 60
4p− S. 22
18p− S. 28
18q− S. 30

Microstomia

Frequent in
Hallermann-Streiff S. 72
Oto-Palato-Digital S. 150
Robinow S. 86
Trisomy 18 S. 10

Occasional in
Hypoglossia-Hypodactyly S. 142
Treacher Collins S. 134

Macrostomia

Frequent in
Facio-Auriculo-Vertebral Anomalad 136
Morquio S. 272
Scheie S. 275
18p− S. 28

Occasional in
Beckwith-Wiedemann S. 94
Treacher Collins S. 134
Williams S. 54
18q− S. 30

Cleft Palate or Bifid Uvula without Cleft in Lip

Frequent in
Cerebro-Costo-Mandibular S. 354
Dubowitz S. 62
Femoral Hypoplasia-Unusual Facies S. 170
Meckel-Gruber S. 96
Oral-Facial-Digital S. 144
Oto-Palato-Digital S. 150
Robin Anomalad 130
Spondyloepiphyseal Dysplasia Congenita S. 194
Stickler S. 154
Treacher Collins S. 134

Occasional in
Aminopterin S. 340
Apert S. 242
Camptomelic Dwarfism S. 184
Cleidocranial Dysostosis S. 230
Coffin-Siris S. 348
Cri-du-Chat S. 24
De Lange S. 56
Diastrophic Dwarfism S. 202
Fetal Alcohol S. 336
Facio-Auriculo-Vertebral Anomalad 136
Hypoglossia-Hypodactyly S. 142
Larsen S. 156
Marfan S. 276
Mohr S. 146
Robinow S. 86
Saethre-Chotzen S. 236
Smith-Lemli-Opitz S. 82
Trisomy 13 S. 14
Trisomy 18 S. 10
XXXXY S. 40
4p− S. 22
18q− S. 30

Oral Frenula (Webs)

Frequent in
Ellis-van Creveld S. 200
Hypoglossia-Hypodactyly S. 142
Oral-Facial-Digital S. 144

Occasional in
Frontonasal Dysplasia Anomalad 128
Mohr S. 146
Opitz-Frias S. 84
Popliteal Web S. 140

Cleft or Irregular Tongue

Frequent in
Cerebro-Costo-Mandibular S. 354
Facio-Auriculo-Vertebral Anomalad 136
Mohr S. 146
Multiple Neuroma S. 314
Oral-Facial-Digital S. 144

Occasional in
Meckel-Gruber S. 96
Trisomy 13 S. 14

Macroglossia

Frequent in
Athyrotic Hypothyroidism Anomalad 372
Beckwith-Wiedemann S. 94
Generalized Gangliosidosis S. 260

Occasional in
Hurler S. 264
Maroteaux-Lamy Mucopolysaccharidosis S. 268
Robinow S. 86
Scheie S. 275

Hypertrophied Alveolar Ridges

Frequent in
Generalized Gangliosidosis S. 260
Hunter S. 270
Hurler S. 264
Leroy I-Cell S. 262
Robinow S. 86

12. TEETH

Anodontia (Aplasia)

Frequent in
- Albright Hereditary Osteodystrophy S. 254
- Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. 326
- Cleidocranial Dysostosis S. 230
- EEC S. 162
- Ellis-van Creveld S. 200
- Gorlin Fronto-Metaphyseal Dysplasia S. 222
- Hallermann-Streiff S. 72
- Johanson-Blizzard S. (partial) 68
- Maroteaux-Lamy Pyknodysostosis S. 228
- Oto-Palato-Digital S. (partial) 150
- Rieger S. (partial) 352
- Robinson Nail Dystrophy-Deafness S. 328
- Van der Woude S. 138
- Williams S. (partial) 54
- Hypohidrotic Ectodermal Dysplasia S. 324

Occasional in
- Crouzon S. (partial) 234
- Ehlers-Danlos S. (partial) 284
- Mohr S. (partial) 146
- Rothmund-Thomson S. 74
- Seckel S. 70

Hypodontia (including Conical Teeth)

Frequent in
- Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. (conical) 326
- Cleft Lip and Palate Anomalad 132
- Down S. 6
- EEC S. 162
- Ellis-van Creveld S. 200
- Goltz S. 320
- Hallermann-Streiff S. 72
- Incontinentia Pigmenti S. (conical) 298
- Johanson-Blizzard S. 68
- Maroteaux-Lamy Pyknodysostosis S. 228
- Osteogenesis Imperfecta Syndromes 286, 288
- Rapp-Hodgkin Ectodermal Dysplasia S. 327
- Rieger S. 352
- Robinson Nail Dystrophy-Deafness S. (conical) 328
- Stanesco Dysostosis S. 232
- Tricho-Dento-Osseous S. 330
- Van der Woude S. 138
- Weill-Marchesani S. 257
- Williams S. 54

Occasional in
- Ehlers-Danlos S. 284
- Linear Sebaceous Nevus Anomalad 296
- Rothmund-Thomson S. 74
- Seckel S. 70
- Sjögren-Larsson S. 100
- XXXXY S. 40

Enamel Hypoplasia

Frequent in
- Albright Hereditary Osteodystrophy S. 254
- Cleidocranial Dysostosis S. 230
- Goltz S. 320
- Hypophosphatasia S. 218
- Morquio S. 272
- Oculodentodigital S. 148
- Prader-Willi S. 106
- Pseudo-Vitamin D Deficiency Rickets (postnatal onset) 216
- Stanesco Dysostosis S. 232
- X-Linked Hypophosphatemic Rickets 214

Occasional in
- Oral-Facial-Digital S. 144
- Sjögren-Larsson S. 100

Carious

Frequent in
- Basal Cell Nevus S. 316
- Cleidocranial Dysostosis S. 230
- Cockayne S. 80
- Dubowitz S. 62
- Dyskeratosis Congenita S. 322
- Hyperphosphatasia-Osteoectasia S. 220
- Hypoglossia-Hypodactyly S. 142
- Oral-Facial-Digital S. 144
- Osteogenesis Imperfecta Syndromes 286, 288
- Prader-Willi S. 106
- Pyle Metaphyseal Dysplasia S. 225

Early Loss of Teeth

Frequent in
- Hajdu-Cheney S. 221
- Hypophosphatasia S. 218
- Werner S. 78

Irregular Placement of Teeth

Frequent in
- Basal Cell Nevus S. 316
- Down S. 6
- Dyskeratosis Congenita S. 322
- Goltz S. 320
- Hallermann-Streiff S. 72
- Hurler S. 264
- Maroteaux-Lamy Pyknodysostosis S. 228
- Morquio S. 272
- Progeria S. 76
- Robinow S. 86
- Tricho-Dento-Osseous S. 330
- Weill-Marchesani S. 257

Occasional in
- Crouzon S. 234
- Ehlers-Danlos S. 284
- Homocystinuria S. 280
- Maroteaux-Lamy Mucopolysaccharidosis S. 268
- Stickler S. 154

Late Eruption of Teeth

Frequent in
- Albright Hereditary Osteodystrophy S. 254
- Cleidocranial Dysostosis S. 230
- Dubowitz S. 62
- Ellis-van Creveld S. 200
- Gardner S. 312
- Goltz S. 320
- Hunter S. 270
- Incontinentia Pigmenti S. 298
- Osteogenesis Imperfecta Syndromes 286, 288
- Progeria S. 76
- X-Linked Hypophosphatemic Rickets 214

Neonatal Teeth

Frequent in
- Ellis-van Creveld S. 200

Hallermann-Streiff S. ... 72
Pachyonychia Congenita S. ... 332

Occasional in
Meckel-Gruber S. ... 96

Dental Cysts

Frequent in
Basal Cell Nevus S. ... 316
Gardner S. ... 312

Occasional in
Lowe S. ... 112

Other Tooth Anomalies

Frequent in
Cohen S. (prominent maxillary central incisors) ... 108
Gardner S. (supernumerary teeth) ... 312
Marshall S. (prominent upper teeth) ... 92
Oral-Facial-Digital S. (anomalous anterior teeth) ... 144
Tricho-Dento-Osseous S. (taurodontism) ... 330
X-Linked Hypophosphatemic Rickets (large pulp chamber, gingival and periapical infections) ... 214
XXY S. (large teeth) ... 38

Occasional in
Oral-Facial-Digital S. (supernumerary teeth) ... 144

13. EXTERNAL EARS

Low-Set Ears

Frequent in
Aminopterin S. ... 340
Treacher Collins S. ... 134
Triploidy S. ... 20
Trisomy 18 S. ... 10
13q− S. ... 26

Occasional in
Camptomelic Dwarfism S. ... 184
Carpenter S. ... 240
Coloboma of Iris-Anal Atresia S. ... 34
Cri-du-Chat S. ... 24
Cutis Laxa-Growth Deficiency S. ... 358
Down S. ... 6
Fetal Hydantoin S. ... 346
Frontonasal Dysplasia Anomalad ... 128
Facio-Auriculo-Vertebral Anomalad ... 136
Schwartz S. ... 116
Trisomy 13 S. ... 14
XXXXX S. ... 44
XXXXY S. ... 40
4p− S. ... 22
18q− S. ... 30

Malformed Auricles

Frequent in
Aarskog S. ... 52
Aniridia-Wilms' Tumor Association (prominent) ... 390
Beals Auriculo-Osteodysplasia S. ... 258
Beckwith-Wiedemann S. ... 94
Blepharophimosis S. ... 122
Contractural Arachnodactyly S. ("crumpled") ... 278
Cryptophthalmos S. ... 121
Diastrophic Dwarfism S. ... 202
DiGeorge Anomalad ... 374
Down S. (small) ... 6
Ehlers-Danlos S. (hypermobile) ... 284
Facio-Auriculo-Vertebral Anomalad ... 136
Fetal Hydantoin S. ... 346
Fraser S. ... 121
Langer-Giedion S. (large, protruding) ... 158
Meckel-Gruber S. ... 96
Multiple Lentigines S. (prominent) ... 318
Opitz-Frias S. (slanted) ... 84
Roberts S. ... 164
Rubinstein-Taybi S. ... 58
Saethre-Chotzen S. ... 236
Seckel S. ... 70
Smith-Lemli-Opitz S. ... 82
Treacher Collins S. ... 134
Tricho-Rhino-Phalangeal S. (prominent) ... 160
Triploidy S. ... 20
Trisomy 8 S. (prominent, cupped, thick helices) ... 18
Trisomy 13 S. (prominent, slanting) ... 14
Trisomy 18 S. ... 10
Turner S. (prominent) ... 46
Weaver S. (prominent) ... 90
XXXXY S. ... 40
XXY S. (long) ... 38
13q− S. (prominent, slanting) ... 26
18p− S. (prominent, protruding) ... 28
18q− S. (prominent antihelix, antitragus) ... 30
21q− S. (large) ... 32

Occasional in
Bloom S. (prominent) ... 64
Coloboma of Iris-Anal Atresia S. ... 34
EEC S. ... 162
Fanconi Pancytopenia S. ... 174
Opitz S. ... 126
Oral-Facial-Digital S. (milia in skin of auricle) ... 144
Prader-Willi S. ... 106
Robinow S. (posteriorly rotated) ... 86
VATER Association ... 388
Zellweger S. ... 110

Preauricular Tags or Pits

Frequent in
Coloboma of Iris-Anal Atresia S. ... 34
Facio-Auriculo-Vertebral Anomalad ... 136
4p− S. ... 22

Occasional in
Cri-du-Chat S. ... 24
Coffin-Siris S. ... 348
Frontonasal Dysplasia Anomalad ... 128

14. NECK, THORAX, AND VERTEBRAE

Web Neck or Redundant Skin

Frequent in
Klippel-Feil Anomalad ... 375
Noonan S. ... 50
Turner S. ... 46
XXXX S. ... 42
Zellweger S. ... 110
13q− S. ... 26

Occasional in
- Aase S. 177
- Down S. 6
- Distichiasis-Lymphedema S. 359
- Fetal Trimethadione S. 344
- Meckel-Gruber S. 96
- Trisomy 18 S. 10
- XXXXY S. 40
- 18p− S. 28

Nipple Anomaly

Frequent in
- De Lange S. 56
- EEC S. (hypoplastic) 162
- Fetal Hydantoin S. (widely spaced) 346
- Trisomy 18 S. (small, occasionally widely spaced) 10
- Turner S. (widely spaced, small) 46
- Weaver S. (inverted) 90

Occasional in
- Cryptophthalmos S. 121
- Johanson-Blizzard S. 68
- Noonan S. 50
- Smith-Lemli-Opitz S. 82
- 18q− S. 30

Hypoplasia of Clavicles

Frequent in
- Cleidocranial Dysostosis S. 230
- Goltz S. 320
- Holt-Oram S. 172

Occasional in
- Progeria S. 76

Pectus Excavatum or Carinatum

Frequent in
- Aarskog S. 52
- Cartilage-Hair Hypoplasia S. 210
- Coffin-Lowry S. 152
- Homocystinuria S. 280
- Hyperphosphatasia-Osteoectasia S. 220
- Kozlowski Spondylometaphyseal Dysplasia S. 196
- Marfan S. 276
- Morquio S. 272
- Multiple Lentigines S. 318
- Noonan S. 50
- Osteogenesis Imperfecta Syndromes 286, 288
- Oto-Palato-Digital S. 150
- Schwartz S. 116
- Spondyloepiphyseal Dysplasia Congenita S. 194
- Turner S. 46
- XYY S. 36
- 18p− S. 28

Occasional in
- Down S. 6
- Hallermann-Streiff S. 72
- Holt-Oram S. 172
- Lowe S. 112
- Mietens S. 147
- Mohr S. 146
- Robinow S. 86
- Williams S. 54
- XXXXY S. 40

Small Thoracic Cage

Frequent in
- Camptomelic Dwarfism S. 184
- Cerebro-Costo-Mandibular S. 354
- Cleidocranial Dysostosis S. 230
- Ellis-van Creveld S. 200
- Jansen Metaphyseal Chondrodysplasia S. 208
- Jeune Thoracic Dystrophy S. 182
- Lymphopenic Agammaglobulinemia–Short-Limbed Dwarfism S. 186
- Metatropic Dwarfism S. 197
- Thanatophoric Dwarfism S. 180

Occasional in
- Achondroplasia S. 188
- Diastrophic Dwarfism S. 202
- Osteogenesis Imperfecta Syndromes 286, 288
- Pseudoachondroplastic Spondyloepiphyseal Dysplasia S. 192

Rib Defects Other Than Small Thorax

Frequent in
- Basal Cell Nevus S. (bifid, synostoses, hypoplasia) 316
- Cerebro-Costo-Mandibular S. 354
- Fetal Hydantoin S. 346
- Generalized Gangliosidosis (thick) 260
- Hunter S. (thick) 270
- Hurler S. (thick) 264
- Hyperphosphatasia-Osteoectasia S. 220
- Incontinentia Pigmenti S. (extra rib) 298
- Morquio S. 272
- Pyle Metaphyseal Dysplasia S. 225
- Sanfilippo S. (thick) 274
- Seckel S. 70
- Trisomy 13 S. 14

Occasional in
- Aminopterin S. 340
- Down S. 6
- Neurofibromatosis S. (rib fusion) 302
- Robinow S. 86
- Rokitansky Anomalad 382
- Trisomy 18 S. 10
- Turner S. 46
- VATER Association 388
- 18q− S. 30

Scoliosis

Frequent in
- Basal Cell Nevus S. 316
- Coffin-Lowry S. 152
- Cohen S. 108
- Conradi-Hünermann S. 211
- Maroteaux-Lamy Mucopolysaccharidosis S. 268
- Pseudoachondroplastic Spondyloepiphyseal Dysplasia S. 192

Occasional in
- Aarskog S. 52
- Comptomelic Dwarfism S. 184
- Camurati-Englemann S. 282
- Cri-du-Chat S. 24
- Fetal Trimethadione S. 344
- Freeman-Sheldon S. 113
- Hallermann-Streiff S. 72

Larsen S. ... 156
Prader-Willi S. ... 106
Pyle Metaphyseal Dysplasia S. ... 225
Rubinstein-Taybi S. ... 58
Seckel S. ... 70
Stickler S. ... 154
Turner S. ... 46
XXXXY S. ... 40
XXY S. ... 38

Other Vertebral Defects

Frequent in

Achondrogenesis Syndromes ... 178, 179
Achondroplasia S. ... 188
Asymmetric Crying Facies-Cardiac Defect Association ... 120
Camptomelic Dwarfism S. ... 184
Cartilage-Hair Hypoplasia S. ... 210
Cerebro-Costo-Mandibular S. ... 354
Cockayne S. (biconvex flattening) ... 80
Coffin-Lowry S. ... 152
Cohen S. ... 108
Contractural Arachnodactyly S. ... 278
Facio-Auriculo-Vertebral Anomalad ... 136
Generalized Gangliosidosis S. ... 260
Gorlin Fronto-Metaphyseal Dysplasia S. ... 222
Hajdu-Cheney S. ... 221
Hurler S. ... 264
Hyperphosphatasia-Osteoectasia S. ... 220
Hypochondroplasia S. ... 190
Jansen Metaphyseal Chondrodysplasia S. ... 208
Jeune Thoracic Dystrophy S. ... 182
Klippel-Feil Anomalad ... 375
Kozlowski Spondylometaphyseal Dysplasia S. ... 196
Leroy I-Cell S. ... 262
Maroteaux-Lamy Mucopolysaccharidosis S. ... 268
Metatropic Dwarfism S. ... 197
Morquio S. ... 272
Multiple Epiphyseal Dysplasia S. ... 206
Osteogenesis Imperfecta S., Autosomal Recessive ... 288
Oto-Palato-Digital S. ... 150
Progeria S. ... 76
Pseudoachondroplastic Spondyloepiphyseal Dysplasia S. ... 192
Pyle Metaphyseal Dysplasia S. ... 225
Rhizomelic Chondrodysplasia Punctata S. ... 212
Robinow S. ... 86
Sanfilippo S. ... 274
Schwartz S. ... 116
Stickler S. ... 154
Thanatophoric Dwarfism S. ... 180
VATER Association ... 388
X-Linked Spondyloepiphyseal Dysplasia S. ... 204

Occasional in

Aarskog S. ... 52
Acrodysostosis S. ... 253
Basal Cell Nevus S. (fusions) ... 316
Coffin-Siris S. ... 348
Conradi-Hünermann S. ... 211
Cri-du-Chat S. ... 24
Diastrophic Dwarfism S. ... 202
Down S. ... 6
Hallermann-Streiff S. (spina bifida) ... 72
Incontinentia Pigmenti S. ... 298
Larsen S. ... 156
Marfan S. ... 276
Nail-Patella S. (spina bifida) ... 248
Neurofibromatosis S. ... 302
Noonan S. ... 50
Osteogenesis Imperfecta Syndromes ... 286, 288
Popliteal Web S. (spina bifida) ... 140
Radial Aplasia-Thrombocytopenia S. ... 176
Rokitansky Anomalad ... 382
Rubinstein-Taybi S. ... 58
Saethre-Chotzen S. ... 236
Trisomy 8 S. ... 18
Trisomy 18 S. ... 10
21q− S. ... 32

15. LIMBS

Arachnodactyly

Frequent in

Contractural Arachnodactyly ... 278
Gorlin Fronto-Metaphyseal Dysplasia S. ... 222
Marfan S. ... 276
Multiple Neuroma S. ... 314
Stickler S. ... 154

Occasional in

Basal Cell Nevus S. ... 316
Homocystinuria S. ... 280

Short Limbs

Frequent in

Achondroplasia Syndromes ... 188
Acrodysostosis S. ... 253
Aminopterin S. ... 340
Brachydactyly S., Type E ... 256
Cartilage-Hair Hypoplasia S. ... 210
Conradi-Hünermann S. (short femur and/or humerus) ... 211
Diastrophic Dwarfism S. ... 202
Dyschondrosteosis S. ... 252
Ellis-van Creveld S. ... 200
Femoral Hypoplasia-Unusual Facies S. ... 170
Hypochondroplasia S. ... 190
Langer Mesomelic Dwarfism S. ... 252
Lymphopenic Agammaglobulinemia–Short-Limbed Dwarfism S. ... 186
Metatropic Dwarfism S. ... 197
Pseudoachondroplastic Spondyloepiphyseal Dysplasia S. ... 192
Rhizomelic Chondrodysplasia Punctata S. (short humerus and/or femur) ... 212
Robinow S. (forearms) ... 86
Thanatophoric Dwarfism ... 180

Occasional in

Coffin-Siris S. ... 348
De Lange S. ... 56
Hypophosphatasia S. ... 218
Meckel-Gruber S. ... 96

Limb Reduction, Moderate to Gross

Frequent in

Amniotic Band Anomalads ... 166
EEC S. (ectrodactyly) ... 162
Grebe S. ... 179

Hypoglossia-Hypodactyly S. 142
Limb Reduction-Ichthyosis S. 269
Roberts S. 164

Occasional in
De Lange S. 56

Small Hands and Feet, including Brachydactyly

Frequent in
Aarskog S. 52
Achondrogenesis Syndromes 178, 179
Achondroplasia S. 188
Apert S. 242
Brachydactyly S., Type E 256
Carpenter S. 240
De Lange S. 56
Down S. 6
Geleophysic Dwarfism S. 198
Hajdu-Cheney S. (distal digits) 221
Mohr S. 146
Multiple Synostosis S. 244
Prader-Willi S. 106
Robinow S. 86
Saethre-Chotzen S. 236
Stanesco Dysostosis S. 232
Werner S. 78
XXXXX S. 44

Occasional in
Langer-Giedion S. 158
Rothmund-Thomson S. 74

Clinodactyly of Fifth Fingers

Frequent in
Aarskog S. 52
Carpenter S. 240
De Lange S. 56
Down S. 6
Dubowitz S. 62
Langer-Giedion S. 158
Mohr S. 146
Roberts S. 164
Russell-Silver S. 60
Saethre-Chotzen S. 236
Seckel S. 70
XXXX S. 42
XXXXX S. 44
XXXXY S. 40
13q− S. 26

Occasional in
Cri-du-Chat S. 24
Fibrodysplasia Ossificans Congenita S. 290
Laurence-Moon-Biedl S. 350
Meckel-Gruber S. 96
Nail-Patella S. 248
Oral-Facial-Digital S. 144
Prader-Willi S. 106
Robinow S. 86
Rubinstein-Taybi S. 58
Steinert Myotonic Dystrophy S. 114
Williams S. 54
18p− S. 28

Thumb Hypoplasia to Aplasia, Triphalangeal Thumb

Frequent in
Aase S. 177
Fanconi Pancytopenia S. 174
Holt-Oram S. (may be triphalangeal) 172
Radial Aplasia-Thrombocytopenia S. 176
Roberts S. 164
Rothmund-Thomson S. 74
VATER Association 388
13q− S. 26

Occasional in
Aminopterin S. 340
De Lange S. 56
Fibrodysplasia Ossificans Congenita S. 290
Trisomy 18 S. 10

Radius Hypoplasia to Aplasia

Frequent in
Aase S. 177
Holt-Oram S. 172
Radial Aplasia-Thrombocytopenia S. 176
Roberts S. 164
VATER Association 388

Occasional in
De Lange S. 56
Fanconi Pancytopenia S. 174
Geleophysic Dwarfism S. 198
Seckel S. 70
Trisomy 13 S. 14
Trisomy 18 S. 10

Metacarpal Hypoplasia—All Metacarpals

Frequent in
Coffin-Siris S. 348
Cohen S. 108
Cri-du-Chat S. 24
Grebe S. 179
Tricho-Rhino-Phalangeal S. 160

Occasional in
Larsen S. 156
Robinow S. 86

Metacarpal Hypoplasia—Third, Fourth, and/or Fifth

Frequent in
Albright Hereditary Osteodystrophy S. 254
Basal Cell Nevus S. 316
Brachydactyly S., Type E 256
Leri-Weill Dyschondrosteosis S. (fourth) 250
Multiple Exostoses S. (fourth-fifth) 246
Oto-Palato-Digital S. 150
Turner S. 46

Occasional in
Conradi-Hünermann S. 211
Saethre-Chotzen S. (fourth) 236

Metacarpal Hypoplasia-First Metacarpal with Proximal Placement of Thumb

Frequent in
Diastrophic Dwarfism S. 202
Geleophysic Dwarfism S. 198
18q− S. 30

Occasional in
De Lange S. 56
Triploidy S. 20

Metatarsal Hypoplasia

Frequent in
Achondrogenesis Syndromes 178, 179
Cohen S. 108

Brachydactyly S., Type E 256
Grebe S. 179
Leri-Weill Dyschondrosteosis S. 250
Tricho-Rhino-Phalangeal S. 160

Occasional in
Femoral Hypoplasia-Unusual Facies S. 170
Coffin-Siris S. 348
Weaver S. (fourth) 90

Polydactyly

Frequent in
Carpenter S. 240
Ellis-van Creveld S. 200
Meckel-Gruber S. 96
Robinson Nail Dystrophy-Deafness S. 328
Trisomy 13 S. 14

Occasional in
Bloom S. 64
Conradi-Hünermann S. 211
Goltz S. 320
Klippel-Trenaunay-Weber S. 306
Oral-Facial-Digital S. (foot) 144
Rubinstein-Taybi S. 58
Smith-Lemli-Opitz S. 82

Broad Thumb and/or Toe

Frequent in
Apert S. 242
Carpenter S. 240
Larsen S. 156
Leri Pleonosteosis S. 349
Pfeiffer S. 238
Rubinstein-Taybi S. 58
Weaver S. 90

Occasional in
Robinow S. 86
Trisomy 13 S. 14

Syndactyly, Cutaneous or Osseous

Frequent in
Apert S. (with synostosis) 242
Carpenter S. 240
Cryptophthalmos S. 121
De Lange S. (second and third toes) 56
EEC S. 162
Goltz S. 320
Oculodentodigital S. (syndactyly of fourth and fifth fingers, third and fourth toes) 148
Oral-Facial-Digital S. 144
Pfeiffer S. 238
Roberts S. 164
Saethre-Chotzen S. 236
Smith-Lemli-Opitz S. (second and third toes) 82
Triploidy S. (third and fourth fingers) 20

Occasional in
Aminopterin S. 340
Bloom S. 64
Cohen S. 108
Conradi-Hünermann S. 211
Down S. (second and third toes) 6
Fanconi Pancytopenia S. 174
Fetal Hydantoin S. 346
Fibrodysplasia Ossificans Congenita S. (short hallux with synostosis) 290
Hallermann-Streiff S. 72
Hypoglossia-Hypodactyly S. 142
Incontinentia Pigmenti S. 298
Klippel-Trenaunay-Weber S. 306
Laurence-Moon-Biedl S. 350
Meckel-Gruber S. 96
Neurofibromatosis S. 302
Oto-Palato-Digital S. 150
Popliteal Web S. 140
Prader-Willi S. 106
Radial Aplasia-Thrombocytopenia S. 176
Robinson Nail Dystrophy-Deafness S. 328
Russell-Silver S. 60
Trisomy 13 S. 14
Trisomy 18 S. 10
21q− S. 32

Elbow Dysplasia and Cubitus Valgus

Frequent in
Cerebro-Costo-Mandibular S. 354
Larsen S. 156
Nail-Patella S. 248
Noonan S. 50
Oto-Palato-Digital S. 150
Pyle Metaphyseal Dysplasia S. 225
Trisomy 8 S. 18
Turner S. 46
XXXXY S. 40

Occasional in
Aarskog S. 52
Albright Hereditary Osteodystrophy S. 254
Oculodentodigital S. 148
XYY S. 36
Zellweger S. 110
18p− S. 28

Patella Dysplasia

Frequent in
Coffin-Siris S. 348
Hyperphosphatasia-Osteoectasia S. (fixation) 220
Nail-Patella S. 248

Occasional in
Carpenter S. 240
Diastrophic Dwarfism S. 202
Neurofibromatosis S. (absence) 302
Popliteal Web S. 140
Trisomy 8 S. 18

16. LIMBS: NAILS, CREASES, DERMATOGLYPHICS

Nail Hypoplasia or Dysplasia

Frequent in
Cartilage-Hair Hypoplasia S. 210
Coffin-Siris S. 348
Dyskeratosis Congenita S. 322
EEC S. 162
Ellis-van Creveld S. (small) 200
Fetal Hydantoin S. 346
Goltz S. 320
Hajdu-Cheney S. 221
Larsen S. 156
Maroteaux-Lamy Pyknodysostosis S. 228
Nail-Patella S. (hypoplasia) 248
Oto-Palato-Digital S. 150
Pachyonychia Congenita S. (thick) 332
Popliteal Web S. 140
Progeria S. (hypoplasia) 76
Rapp-Hodgkin Ectodermal Dysplasia S. 327

Robinson Nail Dystrophy-Deafness S. 328
Tricho-Rhino-Phalangeal S. 160
Trisomy 13 S. 14
Trisomy 18 S. 10
Turner S. 46
Weaver S. 90
Williams S. 54
21q− S. 32

Occasional in
Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. 326
Incontinentia Pigmenti S. 298
Oto-Palato-Digital S. 150
Rothmund-Thomson S. 74

Single Crease (Simian), Upper Palm

Frequent in
Aarskog S. 52
Cohen S. 108
Cri-du-Chat S. 24
De Lange S. 56
Down S. 6
Fetal Alcohol S. 336
Fetal Hydantoin S. 346
Fetal Trimethadione S. 344
Saethre-Chotzen S. 236
Seckel S. 70
Smith-Lemli-Opitz S. 82
Triploidy S. 20
Trisomy 13 S. 14
Zellweger S. 110
4p− S. 22
18q− S. 30

Occasional in
Coffin-Lowry S. 152
Meckel-Gruber S. 96
Noonan S. 50
Trisomy 18 S. 10
XXXXX S. 44
XXXXY S. 40
Zellweger S. 110
18p− S. 28

Distal Palmar Axial Triradius

Frequent in
Cri-du-Chat S. 24
Down S. 6
Trisomy 13 S. 14
18q− S. 30
21q− S. 32

Occasional in
Albright Hereditary Osteodystrophy S. 254
Rubinstein-Taybi S. 58
Smith-Lemli-Opitz S. 82
Turner S. 46

Low Arch Dermal Ridge Pattern on Majority of Fingertips

Frequent in
Trisomy 18 S. 10
XXXXX S. 44
XXXXY S. 40
4p− S. 22

Occasional in
Trisomy 13 S. 14

Whorl Dermal Ridge Pattern on Majority of Fingertips

Frequent in
Smith-Lemli-Opitz S. 82
18q− S. 30

Occasional in
Turner S. 46

17. LIMBS: JOINTS

Joint Limitation and/or Contractures; Inability to Fully Extend (Other than Foot)

Frequent in
Achondroplasia S. (elbow) 188
Cockayne S. 80
Conradi-Hünermann S. 211
Contractural Arachnodactyly S. (especially in knees, elbows, hands) 278
Diastrophic Dwarfism S. 202
Femoral Hypoplasia-Unusual Facies S. (elbow) 170
Fetal Alcohol S. 336
Generalized Gangliosidosis S. 260
Hunter S. 270
Hurler S. 264
Hypochondroplasia S. 190
Jansen Metaphyseal Chondrodysplasia S. 208
Leri Pleoneosteosis S. 349
Leri-Weill Dyschondrosteosis (elbow, wrist) 250
Leroy I-Cell S. 262
Maroteaux-Lamy Mucopolysaccharidosis S. 268
Metatropic Dwarfism S. 197
Moore-Federman S. 353
Morquio S. (especially hips) 272
Multiple Epiphyseal Dysplasia S. (hip) 206
Multiple Synostosis S. (fusion) 244
Oto-Palato-Digital S. (elbow) 150
Popliteal Web S. 140
Progeria S. 76
Pseudo-Hurler Polydystrophy S. 266
Rhizomelic Chondrodysplasia Punctata S. 212
Sanfilippo S. 274
Scheie S. 275
Schmid Metaphyseal Chondrodysplasia S. 209
Schwartz S. 116
Spondyloepiphyseal Dysplasia Congenita S. 194
Stickler S. 154
Triploidy S. 20
Trisomy 8 S. 18
Trisomy 18 S. 10
Weaver S. (camptodactyly) 90
XXXXY S. 40
Zellweger S. (elbow, knee; camptodactyly) 110

Occasional in
De Lange S. (elbow) 56
Mietens S. (knee) 147
Multiple Exostoses S. 246
Trisomy 13 S. (fingers) 14

Club Foot – Especially Equinovarus Deformity, including Metatarsus Adductus

Frequent in
Aminopterin S. (varus) 340
Diastrophic Dwarfism S. 202
Dubowitz S. 62

Femoral Hypoplasia-Unusual Facies S. 170
Freeman-Sheldon S. (varus with contracted toes) 113
Larsen S. 156
Meckel-Gruber S. 96
Moebius Anomalad 118
Zellweger S. 110
4p− S. 22
13q− S. 26
18q− S. 30

Occasional in
Aarskog S. 52
Bloom S. 64
Conradi-Hünermann S. 211
Ehlers-Danlos S. 284
Ellis-Van Creveld S. (valgus) 200
Generalized Gangliosidosis S. 260
Homocystinuria S. (pes cavus, everted feet) 280
Hunter S. 270
Mietens S. 147
Nail-Patella S. 248
Noonan S. 50
Popliteal Web S. 140
Radial Aplasia-Thrombocytopenia S. 176
Riley-Day S. 361
Schwartz S. 116
Seckel S. 70
Steinert Myotonic Dystrophy S. 114
Trisomy 13 S. 14
Trisomy 18 S. 10
Weaver S. 90
XXXXX S. 44
XXXXY S. 40
Zellweger S. 110
18p− S. 28

Clenched Hand; Index Finger Tending to Overlie the Third, and the Fifth Finger Tending to Overlie the Fourth

Frequent in
Trisomy 18 S. 10

Occasional in
Smith-Lemli-Opitz S. 82
Trisomy 13 S. 14

Joint Hypermotility, and/or Lax Ligaments

Frequent in
Cartilage-Hair Hypoplasia S. 210
Coffin-Lowry S. 152
Cohen S. 108
Down S. 6
Ehlers-Danlos S. 284
Lowe S. 112
Marfan S. 276
Metatropic Dwarfism S. 197
Morquio S. 272
Pseudoachondroplastic Spondyloepiphyseal Dysplasia S. 192
Seckel S. 70
Stickler S. 154

Joint Dislocation

Frequent in
Beals Auriculo-Osteodysplasia S. 258
Coffin-Siris S. 348
Cutis Laxa-Growth Deficiency S. 358
Fetal Hydantoin S. (hip) 346
Hajdu-Cheney S. 221
Langer-Giedion S. 158
Larsen S. (elbow, knee, hip) 156
Oto-Palato-Digital S. (elbow) 150
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Occasional in
Aminopterin S. (hip) 340
Conradi-Hünermann S. 211
Ehlers-Danlos S. 284
Fetal Trimethadione S. (hip) 344
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Neurofibromatosis S. 302
Oculodentodigital S. 148
Osteogenesis Imperfecta S., Autosomal Recessive 288
Popliteal Web S. 140
Riley-Day S. 361
Robinow S. (hip, fingers) 86
Russell-Silver S. 60
Seckel S. (hip) 70
XXXXX S. (elbow) 44
18p− S. 28

18. SKIN AND HAIR

Loose, Redundant Skin

Frequent in
Cerebro-Costo-Mandibular S. 354
Diastrophic Dwarfism S. 202
Langer-Giedion S. 158
Limb Reduction-Ichthyosis S. 169
Lymphopenic Agammaglobulinemia–Short-Limbed Dwarfism S. 186
Weaver S. 90

Altered Skin Pigmentation, Melanomata

Frequent in
Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. (diminished pigment) 326
Basal Cell Nevus S. (nevi) 316
Berardinelli Lipodystrophy S. (hyperpigmentation, especially axillae) 357
Bloom S. (café au lait spots) 64
Chediak-Higashi S. (partial albinism) 363
Conradi-Hünermann S. 211
De Sanctis-Cacchione S. 66
Dyskeratosis Congenita S. (reticular) 322
EEC S. (fair) 162
Fanconi Pancytopenia S. (general increase) 174
Goltz S. (poikiloderma) 320
Incontinentia Pigmenti S. (spidery pigment) 298
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Linear Sebaceous Nevus Anomalad (hyperpigmentation) 296
Maffucci S. (vitiligo) 309
McCune-Albright S. (irregular) 304
Multiple Lentigines S. 318
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Rothmund-Thomson S. (reticular) 74
Tuberous Sclerosis S. 300
Turner S. 46
Waardenburg S. 124
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Occasional in
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- Ataxia-Telangiectasia S. (altered skin or hair pigmentation, café au lait spots) ... 102
- Klippel-Trenaunay-Weber S. (nevi) ... 306
- Linear Sebaceous Nevus Anomalad (nevi) ... 296
- Multiple Lentigines S. (café au lait spots) ... 318
- Noonan S. (nevi) ... 50
- Russell-Silver S. (café au lait spots) ... 60
- 18p− S. (hypopigmentation) ... 28

Thick or Ichthyotic

Frequent in
- Limb Reduction-Ichthyosis S. ... 169

Occasional in
- Oral-Facial-Digital S. ... 144
- Rhizomelic Chondrodysplasia Punctata S. ... 212

Cutis Marmorata, Unusual

Frequent in
- De Lange S. ... 56
- Hypothyroidism Anomalad ... 372

Occasional in
- Klippel-Trenaunay-Weber S. ... 306

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Frequent in
- Dubowitz S. ... 62

Occasional in
- Incontinentia Pigmenti S. ... 298
- 18q− S. ... 30

Hemangiomata and Telangiectasis

Frequent in
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- Bloom S. (telangiectases) ... 64
- De Sanctis-Cacchione S. ... 66
- Fabry S. (nodular Lesions) ... 360
- Goltz S. ... 320
- Klippel-Trenaunay-Weber S. ... 306
- Maffucci S. (hemangiomata) ... 309
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- Roberts S. ... 164
- Rothmund-Thomson S. (telangiectases) ... 74
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- Xeroderma Pigmentosa S. ... 335

Occasional in
- Coffin-Siris S. ... 348
- Diastrophic Dwarfism S. ... 202
- Dyskeratosis Congenita S. (telangiectases) ... 322
- Fetal Alcohol S. ... 336
- Fetal Trimethadione S. ... 344
- Radial Aplasia-Thrombocytopenia S. ... 176
- Rubinstein-Taybi S. ... 58
- Trisomy 13 S. (hemangiomata) ... 14
- Trisomy 18 S. ... 10
- Turner S. ... 46

Photo-sensitive Dermatitis

Frequent in
- Bloom S. ... 64
- Cockayne S. ... 80

Deep Sacral Dimple, Pilonidal Cyst

Frequent in
- Bloom S. ... 64
- Carpenter S. ... 240
- Conradi-Hünermann S. ... 211
- Dubowitz S. ... 62
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- Smith-Lemli-Opitz S. ... 82
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Unusual Acne

Frequent in
- Apert S. ... 242
- Pseudo-Hurler Polydystrophy S. ... 266
- XYY S. ... 36

Alopecia (sparse to absent hair)

Frequent in
- Autosomal Recessive Hypohidrotic Ectodermal Dysplasia S. ... 326
- Björnstad Pili Torti-Deafness S. ... 328
- Cartilage-Hair Hypoplasia S. ... 210
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- Hallermann-Streiff S. ... 72
- Homocystinuria S. ... 280
- Hypohidrotic Ectodermal Dysplasia S. ... 324
- Incontinentia Pigmenti S. ... 298
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- Werner S. ... 78

Occasional in
- Conradi-Hünermann S. ... 211
- Ellis-van Creveld S. ... 200
- Goltz S. ... 320
- Linear Sebaceous Nevus Anomalad ... 296
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- Popliteal Web S. ... 140
- Rothmund-Thomson S. ... 74
- Seckel S. ... 70
- 18p− S. ... 28

Hirsutism

Frequent in
- Berardinelli Lipodystrophy S. ... 357
- Coffin-Siris S. ... 348
- De Lange S. ... 56
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- Trisomy 18 S. ... 10

Occasional in
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- Fetal Alcohol S. ... 336
- Rubinstein-Taybi S. ... 58

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Frequent in
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Dubowitz S. (sparse) ... 62
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Frontonasal Dysplasia Anomalad (widow's peak) ... 128
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Occasional in
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Robinow S. ... 86
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Frequent in
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Occasional in
Aase S. (hepatosplenomegaly) 177
Cockayne S. 80
Homocystinuria S. 280
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Moore-Federman S. 353
Scheie S. 275

Pyloric Stenosis

Frequent in
21q− S. 32

Occasional in
De Lange S. 56
Smith-Lemli-Opitz S. 82
Zellweger S. 110

Incomplete Rotation of Colon (Malrotation)

Occasional in
De Lange S. 56
Down S. 6
Marfan S. 276
Triploidy S. 20
Trisomy 13 S. 14
Trisomy 18 S. 10
Zellweger S. 110

Single Umbilical Artery

Frequent in
Sirenomelia (Mermaid) Anomalad 386
VATER Association 388

Occasional in
Fetal Hydantoin S. 346
Multiple Lentigines S. 318
Trisomy 13 S. 14
Trisomy 18 S. 10
Zellweger S. 110

21. RENAL

Kidney Malformation

Frequent in
Asymmetric Crying Facies-Cardiac Defect Association 120
Johanson-Blizzard S. (hydronephrosis) 68
Meckel-Gruber S. 96
Oligohydramnios Tetrad 384
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Occasional in
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Russell-Silver S. 60
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Trisomy 13 S. 14
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Renal Insufficiency

Frequent in
Fabry S. 360
Lowe S. 112
Nail-Patella S. 248
Zellweger S. (renal tubular dysfunction) 110

Occasional in
Johanson-Blizzard S. 68
Laurence-Moon-Biedl S. 350
Williams S. 54

Hypospadias, or Ambiguous External Genitalia, including Bifid Scrotum

Frequent in
Cryptophthalmos S. 121
Dubowitz S. 62
Fetal Trimethadione S. 344
Opitz S. 126
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Robinow S. 86
Smith-Lemli-Opitz S. 82
Triploidy S. 20
4p− S. 22
13q− S. 26
21q− S. 32

Occasional in
Aarskog S. 52
Ellis-van Creveld S. (epispadias) 200
Fanconi Pancytopenia S. 174
Fetal Hydantoin S. 346
Johanson-Blizzard S. 68
Multiple Lentigines S. 318
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Triploidy S. 20
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XXXXY S. 40
XXY S. 38
XYY S. 36
13q− S. 26

Micropenis, Hypogenitalism, Other than Conditions Cited Above

Frequent in
Carpenter S. 240
Meckel-Gruber S. 96
Noonan S. 50
Prader-Willi S. 106

Robinow S. 86
XXY S. 38
18q– S. 30

Occasional in
Acrodysostosis S. 253
DeLange S. 56
Down S. 6
Fanconi Pancytopenia S. 174
Fetal Hydantoin S. 346
Fibrodysplasia Ossificans Congenita S. 290
Hallermann-Streiff S. 72
Triploidy S. 20
XYY S. 36

Cryptorchidism

Frequent in
Aarskog S. 52
Carpenter S. 240
Cryptophthalmos S. 121
Dubowitz S. 62
Gorlin Fronto-Metaphyseal Dysplasia S. 222
Lowe S. 112
Meckel-Gruber S. 96
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Robinow S. 86
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Seckel S. 70
Smith-Lemli-Opitz S. 82
Triploidy S. 20
Trisomy 13 S. 14
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XXXXY S. 40
4p– S. 22
13q– S. 26
18q– S. 30

Occasional in
Cockayne S. 80
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Hypoplasia of Labia Majora

Frequent in
Robinow S. 86
Trisomy 18 S. 20
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Occasional in
De Lange S. 56
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Bicornuate Uterus and/or Double Vagina

Frequent in
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Occasional in
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23. ENDOCRINE AND METABOLIC

Hypogonadism

Frequent in
De Sanctis-Cacchione S. 66
Down S. 6
Prader-Willi S. 106
Turner S. 46
XXXXY S. 40

Occasional in
Acrodysostosis S. 253
Albright Hereditary Osteodystrophy S. 254
Dyskeratosis Congenita S. 322
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Laurence-Moon-Biedl S. 350
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Noonan S. 50
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Hypothyroidism

Frequent in
Athyrotic Hypothyroidism Anomalad 372
Johanson-Blizzard S. 68

Occasional in
Albright Hereditary Osteodystrophy S. 254
Down S. 6

Other Endocrine Abnormality

Frequent in
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Berardinelli Lipodystrophy S. (virilization) 357
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Occasional in
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Peutz-Jeghers S. (granuloma cell tumor of ovary) 311
Steinert Myotonic Dystrophy S. (goiter) 114
Tuberous Sclerosis S. 300

Diabetes Mellitus

Frequent in
- Berardinelli Lipodystrophy S. ... 357
- Werner S. ... 78

Occasional in
- McCune-Albright S. ... 304
- Prader-Willi S. ... 106
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Frequent in
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Frequent in
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Occasional in
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Frequent in
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- Basal Cell Nevus S. (falx cerebri, cerebellum) ... 316
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Occasional in
- Cockayne S. (intracranial) ... 80

Lipoatrophy (Loss or Lack of Subcutaneous Fat)

Frequent in
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Frequent in
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Occasional in
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Frequent in
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Occasional in
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Frequent in
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- 21q– S. ... 32

Occasional in
- Down S. ... 6

Lymphoreticular Malignancy

Occasional in
- Ataxia-Telangiectasia S. (leukemia) ... 102
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Frequent in
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Prader-Willi S. 106

Occasional in

Albright Hereditary Osteodystrophy 254
Down S. 6
XXXXY S. 40
XXY S. 38

Early Macrosomia, Overgrowth

Frequent in

Beckwith-Wiedemann S. 94
Marshall S. 92
Sotos S. 88
Weaver S. 90

Asymmetry

Frequent in

Asymmetric Crying Facies-Cardiac Defect Association 120
Conradi-Hünermann S. (limbs) 211
Hemihypertrophy-Wilms' Tumor Association 390
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Occasional in

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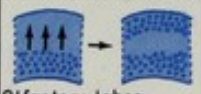
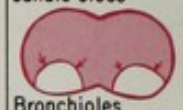
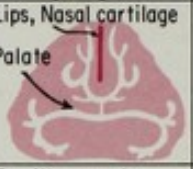
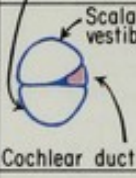
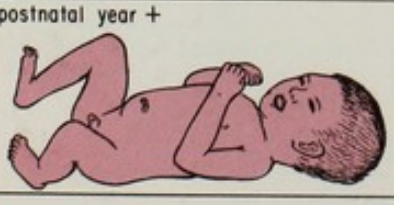
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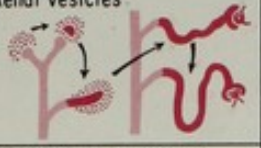
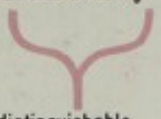
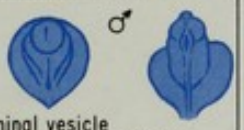
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FETAL DEVELOPMENT

AGE weeks	LENGTH cm. C-R	LENGTH cm. Tot.	WT. gm.	GROSS APPEARANCE	CNS	EYE, EAR	FACE, MOUTH	CARDIO-VASCULAR	LUNG
7	2.8				Cerebral hemisphere  Infundibulum, Rathke's	Lens nearing final shape	Palatal swellings  Dental lamina, Epithel.	Pulmonary vein into left atrium	
8	3.7				Primitive cereb. cortex  Olfactory lobes Dura and pia mater	Eyelid Ear canals	Nares plugged Rathke's pouch detach.  Sublingual gland	A-V bundle Sinus venosus absorbed into right auricle	Pleuroperitoneal canals close  Bronchioles
10	6.0				Spinal cord histology  Cerebellum	Iris Ciliary body Eyelids fuse Lacrimal glands Spiral gland different	Lips, Nasal cartilage Palate 		Laryngeal cavity reopened
12	8.8				 Cord-cervical & lumbar enlarged, Cauda equina	Retina layered Eye axis forward Scala tympani	Tonsillar crypts Cheeks  Dental papilla	Accessory coats, blood vessels	Elastic fibers
16	14				Corpora quadrigemina Cerebellum prominent Myelination begins	 Scala vestibuli Cochlear duct	Palate complete Enamel and dentine	Cardiac muscle condensed	Segmentation of bronchi complete
20						Inner ear ossified	Ossification of nose		Decrease in mesenchyme Capillaries penetrate linings of tubules
24		32	800		Typical layers in cerebral cortex Cauda equina at first sacral level		Nares reopen Calcification of tooth primordia		Change from cuboidal to flattened epithelium Alveoli
28		38.5	1100		Cerebral fissures and convolutions	Eyelids reopen Retinal layers complete Perceive light			Vascular components adequate for respiration
32		43.5	1600	Accumulation of fat		Auricular cartilage	Taste sense		Number of alveoli still incomplete
36		47.5	2600						
38		50	3200		Cauda equina, at L-3 Myelination within brain	Lacrimal duct canalized	Rudimentary frontal maxillary sinuses	Closure of: foramen ovale ductus arteriosus umbilical vessels ductus venosus	
First postnatal year + 					Continuing organization of axonal networks Cerebrocortical function, motor coordination Myelination continues until 2-3 years	Iris pigmented, 5 months Mastoid air cells Coordinate vision, 3-5 months Maximal vision by 5 years	Salivary gland ducts become canalized Teeth begin to erupt 5-7 months Relatively rapid growth of mandible and nose	Relative hypertrophy left ventricle	Continue adding new alveoli

GUT	UROGENITAL	SKELETAL MUSCLE	SKELETON	SKIN	BLOOD, THYMUS LYMPH	ENDOCRINE
Pancreas, dorsal and ventral fusion	Renal vesicles 	Differentiation toward final shape	Cartilaginous models of bones Chondrocranium Tail regression	Mammary gland 		Parathyroid associated with thyroid Sympathetic neuroblasts invade adrenal
Liver relatively large Intestinal villi	Müllerian ducts fusing  Ovary distinguishable	Muscles well represented Movement	Ossification center  Sternum  Joints 	Basal layer 	Bone marrow Thymus halves unite Lymphoblasts around the lymph sacs	Thyroid follicles
Gut withdrawal from cord Pancreatic alveoli Anal canal	Testosterone Renal excretion Bladder sac Müllerian tube into urogenital sinus Vaginal sacs, prostate	Perineal muscles		Hair follicles  Melanocytes	Enucleated R.B.C's Thymus yields reticulum and corpuscles Thoracic duct Lymph nodes; axillary iliac	Adrenalin Noradrenalin
Gut muscle layers Pancreatic islets Bile	♀ ♂  Seminal vesicle Regression, genital ducts		Tail degenerated Notochord degenerated	Corium, 3 layers Scalp, body hair Sebaceous glands Nails beginning	Blood principally from bone marrow Thymus-medullary and lymphoid	Testicle-Leydig cells Thyroid-colloid in follicle Anterior pituitary acidophilic granules Ovary-prim. follicles
Omentum fusing with transverse colon Mesoduodenum, asc. & desc. colon attach to body wall. Meconium. Gastric, intest. glands	Typical kidney Mesonephros involuting Uterus and vagina Primary follicles	In-utero movement can be detected	Distinct bones	Dermal ridges hands Sweat glands Keratinization		Anterior pituitary-basophilic granules
	No further collecting tubules			Venix caseosa Nail plates Mammary budding	Blood formation decreasing in liver	
						Testes-decrease in Leydig cells
						Testes descend
	Urine osmolarity continues to be relatively low			Eccrine sweat Lanugo hair prominent Nails to fingertips		
			Only a few secondary epiphyseal centers ossified in knee		Hemoglobin 17-18 gm Leukocytosis	
			Ossification of 2nd epiph. centers-hamate, capitate, proximal humerus, femur New ossif. 2nd epiph. centers till 10-12 yrs. Ossif. of epiphyses till 16-18 yrs.	New hair, gradual loss of lanugo hair	Transient (6 wk) erythroid hypoplasia Hemoglobin 11-12 gm 7S gamma globulin produced by 6 wks. Lymph nodes develop cortex, medulla	Transient estrinization Adrenal-regression of fetal zone Gonadotropin with feminization of ♀ 9-12 yr. (onset); masc. of ♂ 10-14 yr. (onset)