Dysmorphology terminology and genetic syndromes

Ayman El-Hattab, MD, FAAP, FACMG
Consultant, Genetics and Metabolic
The Division of Clinical Genetics and Metabolic Disorders
Pediatric Department, Tawam Hospital
• Dysmorphology:
  – The study of structural defects (congenital malformations, birth defects) that affect the anatomy (morphology) of the individual.
• Minor anomalies are 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 malformation.

• These minor external anomalies are most common in areas of complex and variable features, such as the face, auricles, hands, and feet.
With one or more major malformations (%)

Number of minor malformations per newborn

0 (85%) 1 (13.4%) 2 (0.8%) 3 or more (0.5%)

90% Mostly multiple major anomalies

% of babies
• Epicanthus
• Up-slanted palpebral fissures
• Down-slanted palpebral fissures
• Hypertelorism
• Brushfeild spots
- Preauricular tag
- Preauricular pit
- Asymmetric ears
- Low-set ears
• Single palmar crease
• Clinodactyly
• Syndactyly
• In addition, before ascribing significance to a given minor anomaly in a patient, it is important 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.
• A pit on the chin in a father and daughter
• Approach for evaluating individuals with birth defects:
  1. Information gathering
  2. Interpret the anomalies
  3. Attempting to arrive to a specific diagnosis
• Gathering information:
  – Family history
  – Prenatal history
  – Birth history
  – Growth parameters
  – Physical examination
  – Measurements (e.g. ear, hand, …)
• Interpret the anomalies:
  – Sequence: a single problem in morphogenesis that leads to a cascade of subsequent defects
• Four categories:
• Malformation sequence: a single localized poor formation of tissue that initiate a chain of subsequent defects (recurrent risk 1-5%).

• Deformation sequence: there is no problem in the fetus but mechanical forces such as uterine constrains result in altered morphogenesis e.g. oligohydraminos (recurrent risk is very low)
• Disruptive sequence: the normal fetus is subjected to a destructive problem (vascular, infectious, mechanical) and its consequences (e.g. amniotic band).

• Dysplasia sequence: the primary defect is a lack of normal organization of cells into tissues (e.g. skeletal dysplasia)
• Malformation syndrome:
  – Multiple structural defects that cannot be explained on basis of a single initiating defect and its consequences but rather appear to be the consequence of multiple defects in one or more tissues.
  – Due to a single cause: chromosomal abnormalities, mutant gene, or teratogenes.
Malformation terminology

http://research.nhgri.nih.gov/morphology/index.cgi

Elements of Morphology: Human Malformation Terminology

An international group of clinicians working in the field of dysmorphology has initiated the standardization of terms used to describe human morphology. The goals are to standardize these terms and reach consensus regarding their definitions. In this way, we will increase the utility of descriptions of the human phenotype and facilitate reliable comparisons of findings among patients.

Discussions with other workers in dysmorphology and related fields, such as developmental biology and molecular genetics, will become more precise. Here we describe the general background of the project and the various issues we have tried to take into account in defining the terms. Published 2009 Wiley-Liss, Inc.

This Web site contains six articles that describe the initial results of a project intended to develop accurate and clear definitions of terms for the craniofacies in general, the major components of the face, and the hands and feet [Allanson et al., [2009]; Biesecker et al., [2009]; Carey et al., [2009]; Hall et al., [2009]; Hennekam et al., [2009]; Hunter et al., [2009]]. These articles are the result of a significant amount of
Head and Face
• Brachycephaly: shortened anteroposterior dimension (length) of the head compared to width

• Dolichocephaly: increased anteroposterior length of the head compared to width
• Occiput, Flat: Reduced convexity of the occiput (posterior part of skull)

• Occiput, Prominent: Increased convexity of the occiput (posterior part of the skull)
• Plagiocephaly: Asymmetric head shape, which is usually a combination of unilateral occipital flattening with ipsilateral frontal prominence, leading to rhomboid cranial shape
• Face, Coarse: Absence of fine and sharp appearance of brows, nose, lips, mouth and chin, usually because of rounded and heavy features or thickened skin with or without thickening of subcutaneous and bony tissues
• Face, Broad: An apparent increase in the width of the face

• Face, Long: An apparent increase in the height (length) of the face

• Face, Narrow: An apparent reduction in the width of the upper and lower face
• Face, Round: Facial appearance is more circular than usual, as viewed from the front

• Face, Square: Facial contours, as viewed from the front, show a broad upper face/cranium and lower face/mandible, creating a square appearance

• Face, Triangular: Facial contour, as viewed from the front, triangular in shape, with breadth at the temples and tapering to a narrow chin
• Forehead, Broad: Apparently increased distance between the two sides of the forehead

• Forehead, Narrow: Apparently narrow inter-temporal region
• Forehead, Prominent: Forward prominence of the entire forehead, due to protrusion of the frontal bone.

• Frontal Bossing: Bilateral bulging of the lateral frontal bone prominences with relative sparing of the midline
• Midface Prominence: Anterior positioning of the infraorbital and perialar regions, or increased convexity of the face
• Midface Retrusion: Posterior positioning and/or vertical shortening of the infraorbital and perialar regions, or increased concavity of the face.
• Neck, Broad: Increased width of the neck when viewed from the front or back
• Neck Webbing: A paravertically oriented fold of skin on the posterolateral aspect of the neck
• Neck, Long: Increased distance from the point where neck and shoulders meet to the inferior margin of the occipital bone

• Neck, Short: Decreased distance from the point where neck and shoulders meet to the inferior margin of the occipital bone
• Nuchal Skin, Redundant: Excess skin around the neck, often lying in horizontal folds
• Palpebral Fissure, Down-slanted: The inclination of the palpebral fissure is less than typical for age

• Palpebral Fissure, Up-slanted: The inclination of the palpebral fissure is greater than typical for age
• Palpebral Fissure, Short: reduced length of the palpebral fissures

• Palpebral Fissure, Long: Apparently increased length of the palpebral fissures.
• Palpebral Fissure, Almond-Shaped: A shape created by an acute downward arching of the upper eyelid and upward arching of the lower eyelid, toward the medial canthus, which gives the outline of the palpebral fissures the configuration of an almond; thus, the maximum distance between the fissures is offset from, and medial to, the center point.
• **Proptosis**: An eye that is protruding anterior to the plane of the face to a greater extent than is typical

• **Eye, Deeply Set**: An eye that is more deeply recessed into the plane of the face than is typical
FACIAL MEASUREMENTS

INNER CANTHAL DISTANCE

in  cm
3.5
1.25
3.0
2.5
2.0
1.5
0.75
0.50

MONTHS

YEARS

AGE

0  3  6  9  12  15  18  21  2  3  4  5  6  7  8  9  10  11  12  13  14

%  97%

75
50
25
3

B
• Telecanthus (Dystopia Canthorum): increased distance between the inner canthi
• Eyes, Widely Spaced (hypertelorism): The interpupillary distance appears to be increased

• Eyes, Closely Spaced (hypotelorism): The interpupillary distance appears to be decreased
• Epicanthus: A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus
• Ptosis: The upper lid margin obscures at least part of the pupil

• Upper Eyelid fullness: Swelling or distention of the upper eyelid

• Synophrys: Meeting of the medial eyebrows in the midline
• **Microtia, First Degree:** Presence of all the normal ear components and the median longitudinal length more than 2 SD below the mean

• **Microtia, Second Degree:** Median longitudinal length of the ear more than 2 SD below the mean in the presence of some, but not all, parts of the normal ear

• **Microtia, Third Degree:** Presence of some auricular structures, but none of these structures conform to recognized ear components

• **Anotia:** Complete absence of any auricular structures
• Ear, Long: increased length of the ear
• Ear, Protruding: Angle formed by the plane of the ear and the mastoid bone greater than the 97th centile for age OR Outer edge of the helix more than 2 cm from the mastoid at the point of maximum distance

• Ear, Cupped: Laterally protruding ear that lacks antihelical folding (including absence of inferior and superior crura)

• Ear, Crumpled: Distortion of the course of the normal folds of the ear and the appearance of supernumerary crura and folds
• Ear, Low-Set: Upper insertion of the ear to the scalp below an imaginary horizontal passing through the inner canthi and extend that line posteriorly to the ear
• Ear, Posterior Angulation, Increased: increased angle formed by the perpendicular line and the medial longitudinal axis of the ear
• Pit, Auricular: Small indentation in the ear

• Pit, Preauricular: Small indentation anterior to the insertion of the ear
• Tag, Auricular: Small protrusion within the pinna

• Tag, Preauricular: Small non-cartilaginous protrusion anterior to the insertion of the ear
• Nose, Long: increased length from the nasal root to the nasal base

• Nose, Short: decreased length from the nasal root to the nasal tip
• Nasal Bridge, Depressed: Posterior positioning of the nasal root in relation to the overall facial profile for age

• Nasal Bridge, Prominent: Anterior positioning of the nasal root in comparison to the usual positioning for age
• Philtrum, Long: increased distance between nasal base and midline upper lip vermilion border.

• Philtrum, Short: decreased distance between nasal base and midline upper lip vermilion border
• Philtrum, Smooth: Flat skin surface, with no ridge formation in the central region of the upper lip between the nasal base and upper vermilion border

• Philtrum, Deep: Accentuated, prominent philtral ridges giving rise to an exaggerated groove in the midline between the nasal base and upper vermilion border
• Upper Lip, Thick: increased height of the vermilion of the upper lip in the frontal view

• Lower Lip, Thick: increased height of the vermilion of the lower lip in the frontal view
• Upper Lip, Thin: reduced height of the vermilion of the upper lip in the frontal view

• Lower Lip, Thin: reduced height of the vermilion of the lower lip in the frontal view
• Upper Lip, Tented: Triangular appearance of the oral aperture with the apex in the midpoint of the upper vermilion and the lower vermilion forming the base

• Lip Pit: Depression located on the vermilion of the lower lip, usually paramedian
• Mouth, Wide (Macrostomia, Large Mouth): increased width of the oral aperture

• Mouth, Narrow (Microstomia, Small Mouth): decreased width of the oral aperture
• Retrognathia: Posteriorly positioned lower jaw, which is set back from the plane of the face when viewed from the side but not from the front

• Prognathism: Anterior protrusion of the mandibular alveolar ridge beyond the vertical plane of the maxillary alveolar ridge, best appreciated in profile
• Micrognathia: Apparently reduced length and width of the mandible when viewed from the front but not from the side
• Hands and feet
• **Finger, Short (Brachydactyly):** fingers that appear disproportionately short compared to the hand

• **Fingers, Long (Arachnodactyly):** fingers that appear disproportionately long compared to the hand
• Finger, Slender (Narrow, Arachnodactyly, Thin): Digits are disproportionately narrow (reduced girth) for the hand/foot size or build of the individual.

• Finger, Broad (Wide, Thick): Increased width of a non-thumb digit of the hand
• Finger, Absent:  
The absence of all phalanges of a digit of the hand and the associated soft tissues
• (Oligodactyly)
• Clinodactyly: A digit that is laterally curved in the plane of the palm
• Camptodactyly: The DIPJ and/or PIPJ of the fingers cannot be fully extended by either active or passive extension
• Fingers, Overlapping: A finger resting on the dorsal surface of an adjacent digit when the hand is at rest
• Fingers, Cutaneous Syndactyly of: A soft tissue continuity in the A/P axis between two fingers that lies significantly distal to the flexion crease that overlies the metacarpophalangeal joint of the adjacent fingers.
• Hand, Preaxial Polydactyly of: Duplication of all or part of the first ray
• Hand, Postaxial Polydactyly of: Presence of a supernumerary digit that is not a thumb
• Hand, Polydactyly, Mesoaxial: The presence of a supernumerary finger (not a thumb) involving the third or fourth metacarpal with associated osseous syndactyly
• Hand, Small: A normally proportioned hand (i.e., the various elements of the hand are in proportion to each other) that is overall small for age or overall body size
• Hand, Clenched: All digits held completely flexed at the metacarpophalangeal and interphalangeal joints
• Hand, Split: Longitudinal deficiency of a digital ray of the hand except rays 1 or 5.
• (Cleft Hand, Ectrodactyly)
• Toe, Short (Brachydactyly): Digits that appear disproportionately short compared to the foot

• Toe, Long (Arachnodactyly): Digits that appear disproportionately long compared to the foot
• Toe, Slender (Narrow, Thin, Arachnodactyly): Digits are disproportionately narrow (reduced girth) for the hand/foot size or build of the individual

• Toe, Broad: increase in width of the non-hallux digit without an increase in the dorso-ventral dimension
• Toes, Cutaneous Syndactyly of: A soft tissue continuity in the A/P axis between two digits of the foot that does not meet the prior objective criteria.
• Foot, Preaxial Polydactyly of: Duplication of all or part of the first ray
• Foot, Postaxial Polydactyly of: Presence of a supernumerary digit that is not a hallux
• Foot, Polydactyly, Mesoaxial: The presence of a supernumerary toe (not a hallux) involving the third or fourth metatarsal with associated osseous syndactyly
• Sandal Gap: A widely spaced gap between the first toe (the great toe) and the second toe
• Foot, Split: Longitudinal deficiency of a digital ray of the foot except rays 1 or 5

• (Ectrodactyly)
• Sole, Convex Contour of: The contour of the foot in lateral profile has a convex shape

• Heel, Prominent: Exaggerated or marked projection of the posterior pole of the heel

• Foot, Rocker Bottom: The presence of both a "prominent heel" and a "convex contour of the sole"
• Pes Planus: A foot where the arch is in contact with the ground or floor when the individual is standing

• Pes Cavus: The presence of an unusually high plantar arch
• Palmar Crease, Single Transverse: The distal and proximal transverse palmar creases are merged into a single transverse palmar crease
References:

• Smith’s recognizable patterns of human malformation

• http://research.nhgri.nih.gov/morphology/index.cgi
Trisomy 21 (Down syndrome)

- Craniofacial:
  - Flat facial profile, brachycephaly with flat occiput
  - Microcephaly
  - Upward slanting palpebral fissure with epicanthal folds
  - Open mouth with protruding tongue
  - Short nose with depressed nasal bridge
  - Small, low-set ear with overfolded helix
  - Short neck with excess skin at the back of the neck
Hands and feet:
- Brachydactyly
- Hyopolasia of middle phalanx of 5th finger
- Clinodactyly
- Single palmar crease
• Sandal gap
• Planter crease between first and second toe
– Hypotonia
• Loose skin folds in posterior neck
• Eyes:
  – Brushfield spots (speckling of iris)
  – Iris hypoplasia
  – Refractive errors (mostly myopia)
  – Lens opacities
  – Strabismus
  – Cataract, adults
  – Nystagmus
  – Blocked tear duct
  – Keratoconus
  – Cataract, congenital
• Neurocognitive: Hypotonia, Developmental delay, Seizures (10%)
• Growth: Microcephaly, Short stature, Increased weight in adolescence
• Musculoskeletal: Joint hyperflexibility, vertebral and rib anomalies, Hip anomalies (dysplasia, dislocation), atlantoaxial dislocation
• Eras: Hearing loss, Middle ear fluid
• Cardiac: Endocardial cushion defect, VSD, PDA, ASD, mitral valve, tricuspid, aortic regurgitation (adults)
• Endocrine and genital:
  – Micropenis and decreased testicular volume
  – Primary gonadal deficiency
  – Infertility
  – hypothyroidism
• GI anomalies: TEF, pyloric stenosis, duodenal atresia, imperforate anus
• Sporadic
• Chromosomal analysis (karyotype)
Trisomy 18 (Edwards syndrome)

• Craniofacial
  – Prominent occiput
  – Short palpebral fissures, ptosis, epicanthus, hypertelorism
  – Iris coloboma, corneal opacities, cataract
  – Microphthalmia
  – Narrow forehead
  – Low-set, malformed ears
  – Micrognathia, cleft lip/palate
  – Short neck
Hands and feet:
- Clenched hands, Overlapping fingers
- Nail hypoplasia
- Short hallux, dorsiflexed
- Ulnar or radial deviation of hands
- Hypoplastic or absent thumb
- Single palmar crease
- Rocker bottom feet
- Syndactyly, polydactyly
- Short fifth metacarpal
• Skeletal:
  – Limited hip abduction, Dislocated hip
  – Radial aplasia
  – Short sternum
  – Small pelvis
  – Broad chest with widely spaced nipple
  – Vertebral and rib anomalies
• Growth: microcephaly, growth deficiency
• Neurocognitive:
  – Developmental delay
  – Weak cry
  – Hypertonicity (after neonatal period)
  – Facial palsy
  – Hypomyelination
  – Microgyria
  – Cerebellar hypoplasia
  – Defects of corpus callosum
  – Hydrocephalus
  – Meningomyeloceal
• Genital: Cryptorchidism, Hypospadias, Bifid scrotum, Hypoplasia of labia major with prominent clitoris, Bifid uterus, Ovarian hypoplasia

• Cardiovascular: VSD, ASD, PDA, Bicuspid aortic and pulmonic valves, Pulmonic stenosis, Aortic coarctation, Transposition of great vessels, TOF

• Renal: Horseshoe kidney, Ectopic kidney, Double ureter, Hydronephrosis, Polycystic kidney

• GI: Pyloric stenosis, Biliary atresia, Imperforate anus, TEF
• Sporadic
• Chromosomal analysis (karyotype)
Trisomy 13 (Patau syndrome)

• Craniofacial:
  – Sloping forehead
  – Wide sagittal suture and fontanels
  – Microphthalmia, hypotelorism, upslanting palpebral fissures
  – Absent eyebrows, underdeveloped supraorbital ridges
  – Iris coloboma, retinal dysplasia
  – Low-set malformed ears
  – Micrognathia, cleft lip and palate
• Skin:
  – Capillary hemangioma
  – Scalp defects
  – Loose skin, posterior neck
• Hands and feet:
  – Single palmar crease
  – Hyperconvex narrow finger nails
  – Camptodactyly, polydactyly, syndactyly
  – Posterior prominent heel
  – Ulnar deviation of hands
  – Radial aplasia
• Growth: Microcephaly, Growth deficiency
• Neurocognitive:
  – Holoprosencephaly
  – Seizures
  – Apneic spells
  – Severe developmental delay
  – Deafness
  – Hypotonia/hypertonia
  – Agenesis of corpus callosum
  – Hydrocephalus
  – Cerebellar hypoplasia
  – Meningomyelocele
• Cardiac: VSD, PDA, ASD, Dextrocardia, Anomalous pulmonary venous return, Pulmonary stenosis, Hypoplastic aorta
• Skeletal: Rib anomalies, Pelvis anomalies
• Genital: Cryptorchidism, Abnormal scrotum (scrotalization of phallus), Bicornuate uterus, Hypospadias, Hypoplastic ovaries
• Renal: Polycystic kidney, Hydronephrosis, Horseshoe kidney, Duplicated ureters
• Sporadic
• Chromosomal analysis (karyotype)
Aneuploidy syndromes

- Trisomy 21
- Trisomy 13
- Trisomy 18
Microdeletion syndromes
• Cleft lip and palate
• TOF
• Hypocalcemia
22q11 deletion (DiGeorge) syndrome

- Cleft lip/palate
- Bifid uvula
- Conotruncal heart defects (right-sided aortic arch, TOF, VSD)
- Hypocalcemia cause by hypoparathyroidism
- Abnormal T-cell function caused by thymic hypoplasia
• Hypotonia
• Microcephaly
• Renal anomalies
• Distinctive facial features in neonates:
  – Hypertelorism
  – Ear malformation
  – Anteverted nose
  – Micro-retrognathia
• Later in childhood:
  – Narrow palpebral fissures
  – Prominent nose
  – Square nasal root
  – Malar hypoplasia
  – Hypernasal speech
  – Speech delay
• Mostly de novo
• Chromosomal microarray
• Congenital heart defects: supravalvular aortic stenosis, peripheral pulmonary artery stenosis
• Hypercalcemia
Williams syndrome

- Congenital heart defects: supravalvular aortic stenosis, peripheral pulmonary artery stenosis
- Hypercalcemia
- Hypotonia
- Joint hypermobility and soft lax skin.
- Renal anomalies
• Distinctive facial features are hard to be recognized in neonatal period (periorbital fullness and full lips)
• Developmental delay
• Unique personality: overfriendliness, empathy, generalized anxiety, specific phobias, and attention deficit disorder.
• Mostly de novo
• Chromosomal microarray: 7q11 deletion
Microdeletion syndromes

- 22q11 deletion syndrome
- Williams syndrome
• Craniofacial syndromes
• Syndromes with hypotonia
• Cardiac Syndromes
• Syndromes with macrosomia
• Syndromes with skin findings
• Metabolic syndromes
Craniofacial syndromes
Stickler syndrome

• In neonatal period:
  – Pierre-Robin sequence (cleft palate with micrognathia)
  – Flat face, prominent eyes, short anteverted nose
  – Possible cataract and glaucoma

• Later manifestations:
  – Vitreoretinopathy and retinal detachment
  – Hearing impairment
  – Epiphyseal dysplasia and degenerative joint diseases
• Autosomal dominant
• Great phenotypic variability
• Genetically heterogeneous
• Gene panel
Syndromes with hypotonia
Prader-Willi syndrome

• Neonatal manifestations:
  – Hypotonia
  – Feeding difficulties
  – FTT
  – Bitemporal narrowing, almond-shaped eyes, thin upper lips
  – Central sleep apnea
• Later manifestations:
  – Truncal obesity
  – Voracious appetite
  – Learning and behavioral difficulties
  – Small hands and feet
  – Short stature
• Caused by:
  – Paternal deletion of 15q11q13 (75%)
  – Maternal UPD (24%)
  – Imprinting defects

• Methylation test for Prader-Willi/ Angelman syndrome
Syndromes with hypotonia

- Prader Willi syndrome
- Spinal muscular atrophy
- Myotonic dystrophy
Noonan syndrome

• Neonatal manifestations:
  – Tall forehead with course facial features
  – Ptosis with thick droopy eyelids
  – Hypertelorism and epicathal folds
  – Blue or blue-green iris
  – Low-set posteriorly rotated ears
  – Short neck with excess nuchal skinfolds
• Cardiac manifestations:
  – Hypertrophic cardiomyopathy
  – Pulmonic stenosis
  – Septal defects
• Lymphedema of dorsum of hands and feet
• Hypotonia
• Joint laxity
• Cryptorchidism
• Feeding difficulty
• FTT
• Later manifestations:
  – Short stature
  – Microcephaly
• Autosomal dominant or de novo
• Genetically heterogeneous
• Gene panel
Cardiac Syndrome

- Noonan syndrome and other RAS-related disorders
- Neonatal Marfan syndrome
- CHARGE syndrome
Beckwith-Wiedemann syndrome

• Manifestations in neonatal period:
  – Macrosomia
  – Macroglossia
  – Abdominal wall defects
  – Hypoglycemia
  – Ear lobe creases and pits of posterior helix
  – Visceromegaly
  – Hemihyperplasia
  – Renal and cardiac defects
• Facial features:
  – Macroglossia
  – Nevus flammeus
  – Infraorbital creases
  – Midface hypoplasia
• Wilms tumors and hepatoblastoma can present in neonatal period
• Caused by epigenetic alterations in 11p15.
• Methylation test for Beckwith-Wiedemann syndrome
Syndromes with skin findings

**Incontinentia pigmenti**
- Affects the skin, hair, teeth, nails, eyes, and central nervous system.
- Characteristic skin lesions evolve through four stages:
Stage I: Blistering (birth to age ~4 months)
Stage II: Wart-like rash (for several months)
Stage III: Swirling macular hyperpigmentation (age ~6 months into adulthood)
Stage IV: Linear hypopigmentation
• Developmental delay
• Seizures
• Microcephaly
• Hypodontia and microdontia
• Sparse hair
• Nail dystrophy
• Retinal lesions
• X-linked dominant or de novo
• Lethal in males
• Genetic test: IKBKG gene
Metabolic syndromes

**Smith-Lemli-Opitz syndrome**

- Cleft palate
- Cardiac defects: atriventricular septal defects, total anomalous pulmonary venous return
- Hypospadias and cryptorchidism
- Post axial polydactyly
- Short thumbs
- Y-shaped second-third toe syndactyly
• Facial features:
  – Microcephaly
  – Ptosis
  – Depressed nasal bridge
  – Short anteverted nose
  – Micrognathia
• Autosomal recessive
• Disorder of cholesterol synthesis.
• Low cholesterol
• DHCR7 gene testing
References


• GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1116/