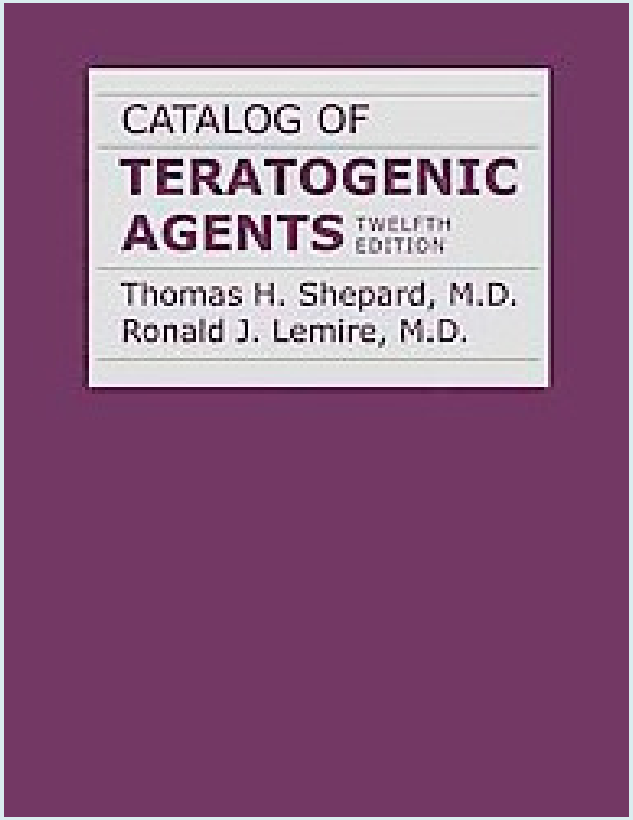
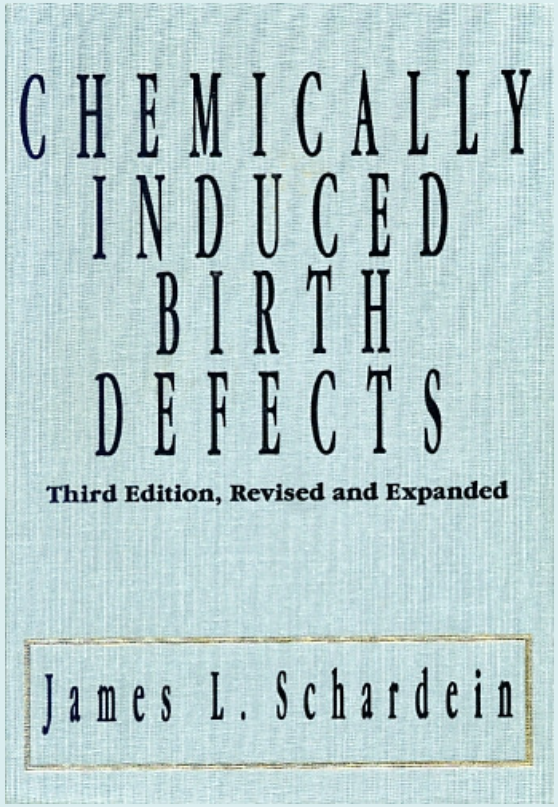
Comparative Aspects of Birth Defects in Laboratory Animals and Humans

Kohei Shiota, MD, PhD

Shiga University of Medical Sciences, Japan


CATALOG OF
TERATOGENIC
AGENTS
TWELFTH
EDITION
Thomas H. Shepard, M.D.
Ronald J. Lemire, M.D.


CHEMICALLY
INDUCED
BIRTH
DEFECTS
Third Edition, Revised and Expanded
James L. Schardein

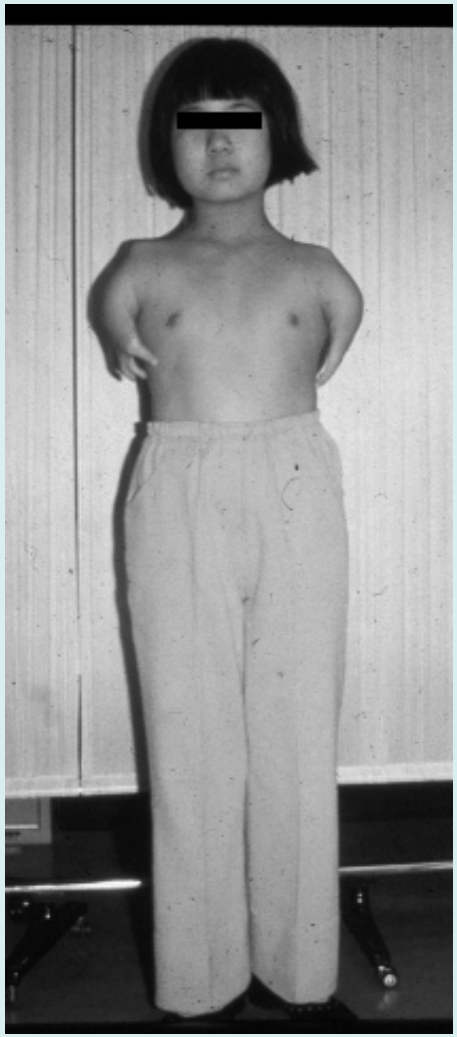
- Over 2,000 agents have been shown to be embryotoxic/teratogenic in one or more animal species.

Identification of Human Teratogens

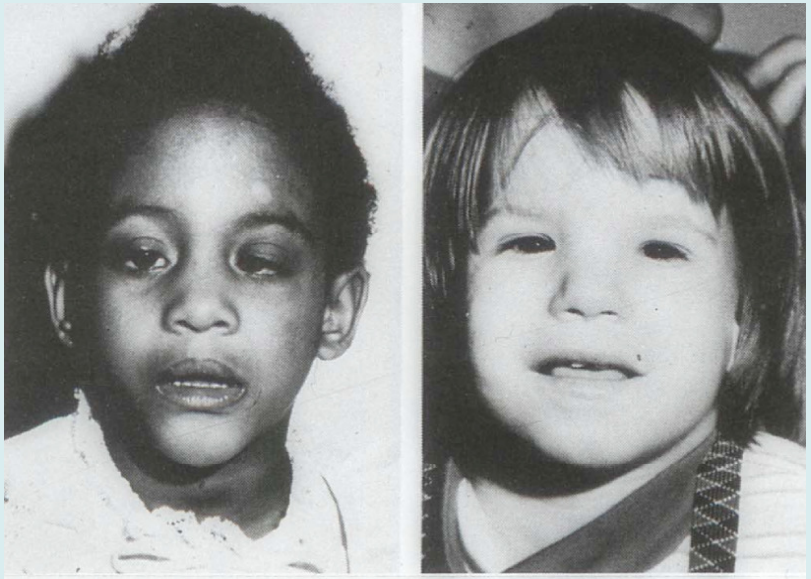
1920s	Radiation
1930s	Endemic cretinism
1940s	Toxoplasmosis, Rubella
1950s	Virilizing tumors
	Cytomegalovirus, Syphilis
	Aminopterin
1960s	Herpes II virus
	Methylmercury
	Diabetes mellitus, Phenylketonuria
	Methotrexate, Cyclophosphamide
	Thalidomide, Busulfan, Progestins
1970s	Venezuelan encephalitis virus, Varicella, Herpes I virus
	Polychlorobiphenyls
	Diethylstilbestrol, Warfarin, Phenytoin, Trimethadione
	Alcohol
	Hyperthermia
1980s~	Parvovirus B19, HIV virus
	Retinoids, Valproic acid, Anti-inflammatory drugs
	Angiotensin-converting enzyme (ACE) inhibitor

- Over 2,000 agents have been shown to be embryotoxic/teratogenic in one or more animal species.

- Only a limited number of those agents have been proven to be embryotoxic/teratogenic in humans.



Thalidomide embryopathy



Fetal alcohol syndrome

- Over 2,000 agents have been shown to be embryotoxic/teratogenic in one or more animal species.

- Only a limited number of those agents have been proven to be embryotoxic/teratogenic in humans.

- Many human teratogens have been identified by clinicians when they observed a small number of patients with birth defects.

Over 2,000 agents have been shown to be embryotoxic/teratogenic in one or more animal species.

Only a limited number of those agents have been proven to be embryotoxic/teratogenic in humans.

Many human teratogens were identified by clinicians when they observed a small number of patients with birth defects.

↓

How accurately can preclinical animal studies predict the embryotoxic/teratogenic risks in humans

Comparison of Teratogenicity in the Human and Laboratory Animals*

Agents teratogenic in humans (N=38)		Agents not teratogenic in humans (N=165)	
Species	Teratogenic (Correctly positive)	Species	Not teratogenic (Correctly negative)
Mouse	58%	Mouse	35%
Rat	80%	Rat	50%
Rabbit	60%	Rabbit	70%
Hamster	45%	Hamster	35%
Nonhuman primate	30%	Nonhuman primate	80%
Two species or more	80%	Two species or more	50%
Any species	97%	All species	28%

*Compiled by US FDA (1980).

Teratogenicity of Major Human Teratogens in Laboratory Animals

Teratogenic agent	Major anomalies induced in humans	Species					
		Mouse	Rat	Giunea pig	Hamster	Rabbit	Nonhuman primate
Ethanol	Craniofacial anomalies, cardiovascular defects	++	+	+		+	++
Aminopterin	Skeletal defects	+	++			-	-
Androgenic hormones	Masculinization in female babies	++	++	++	++	++	++
Coumarin	Nasal dysplasia, skeletal anomalies	-	-			-	
Diethylstilbestrol	Uterine malformations	++	++		-	-	+
Methyl mercury	Microcephaly, neurological disorders	++	++		+	-	+
Streptomycin	Inner ear anomalies	-	++	-		-	
Valproic acid	Neural tube defects, raniofacial anomalies	++	+	+	+	+	+
Thalidomide	Phocomelic defects	+	+	-	+	++	++

-: Not teratogenic; +: Teratogenic; ++: Induces similar anomalies as in humans.

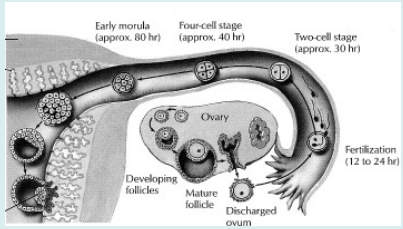
Teratogenic Doses in Humans and Laboratory Animals

	Teratogenic dose (mg/kg/day)				
Teratogen	**Human**	**Mouse**	**Rat**	**Rabbit**	**Nonhuman primate**
Alcohol	**400**		**1500**		
Aminopterin	**0.02**	**0.15**	**0.15**		
DES	**0.02**				**0.2**
Methylmercury	**0.005**	**2**	**0.25**		
Thalidomide	**1**			**150**	**5**
Trimethadione	**12-24**	**600**			**60**
X-ray	**20-50R**	**200R**	**30R**		**250R**

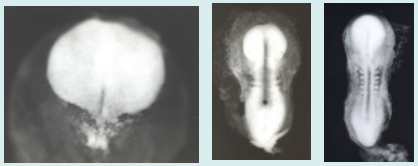
Causes of Species Difference in Teratogenesis

1. **Phylogenetic difference in reproduction and pregnancy**
2. Different susceptibility of embryonic tissues to exogenous agents
3. Species difference in pharmacokinetics in the mother-placenta-embryo complex
    - Placental transfer (rate and extent)
    - Absorption, tissue distribution, metabolism and excretion

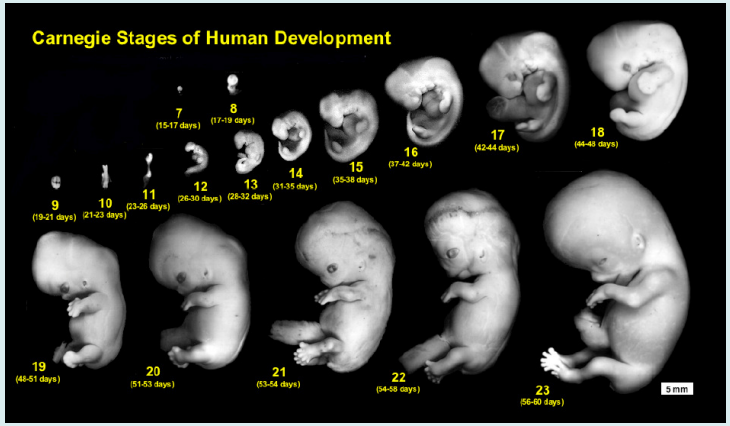
Gametogenesis
Fertilization
Preimplation period
Early development
Organogenesis
Fetal period
Perinatal period



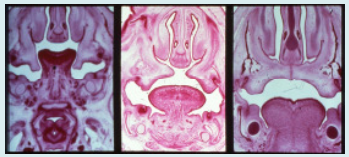
Gene mutations
Chromosomal aberrations



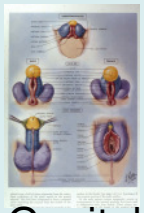
Imprinting disorders



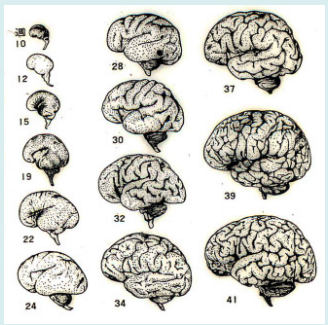
Malformations



Palate



Genital organs



Brain

Abnormal histogenesis

Functional deficits

Species Characteristics of Reproduction

Species	Length of gestation (days)	Duration of reproductive cycle (days)	Critical period of organogenesis (days)
Mouse	19	4-5	7-15
Rat	22	4-5	9-17
Hamster	16	4-15	7-14
Guinea pig	68	13-20	11-25
Rabbit	30	15-16	7-20
Rhesus monkey	165	24-38	20-45
Human	266	26-29	18-55

Placental Types in Different Species

Species	Placenta type
Mouse	Hemotrichorial
Rat	Hemotrichorial
Hamster	Hemotrichorial
Guinea pig	Hemomonochorial
Rabbit	Hemodichorial
Rhesus monkey	Hemomonochorial
Human	Hemomonochorial

Causes of Species Difference in Teratogenesis

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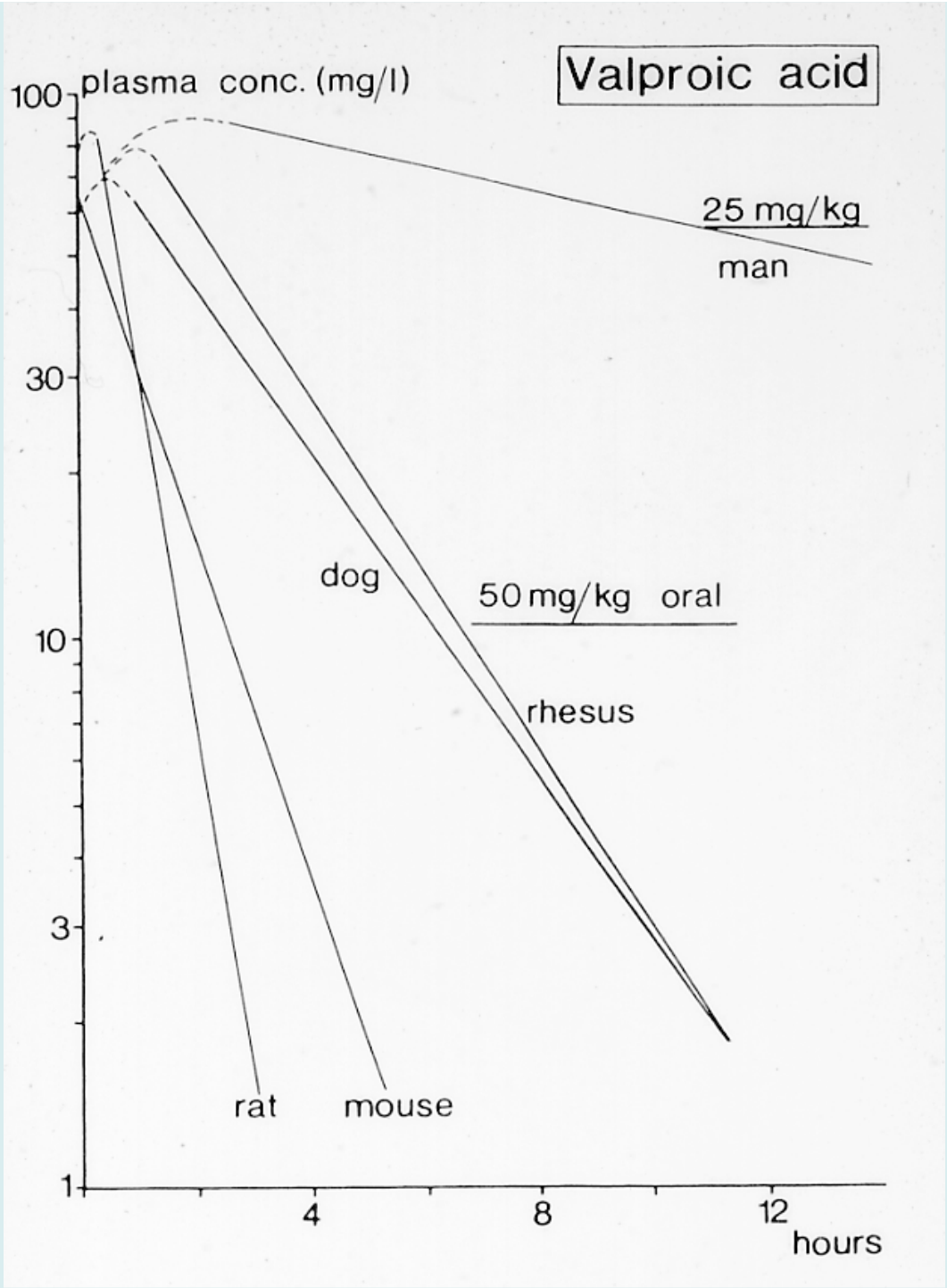
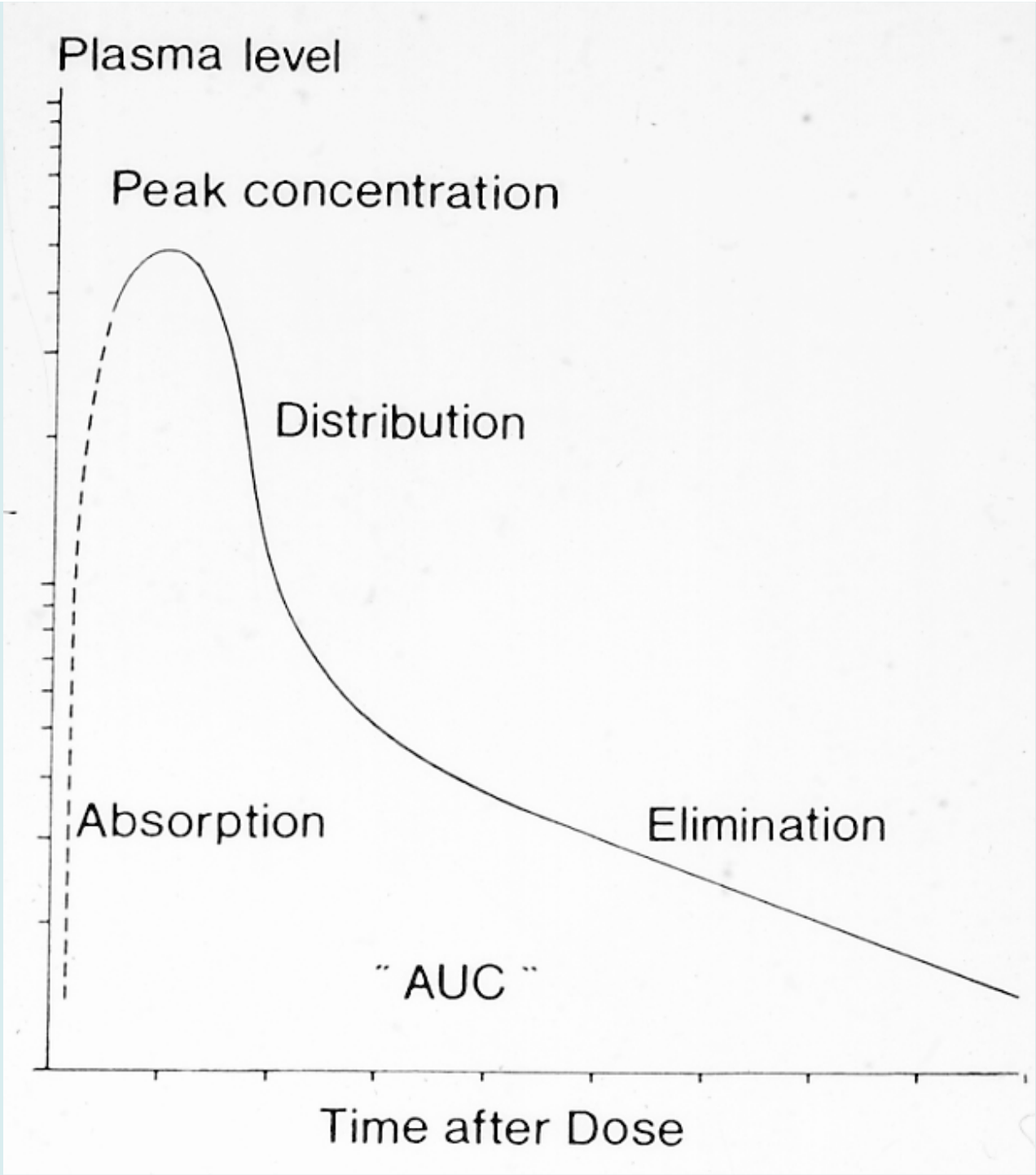

Valproic acid
plasma conc. (mg/l)
100
30
10
3
1
25 mg/kg
man
dog
50 mg/kg oral
rhesus
rat
mouse
4
8
12
hours

Nau (1987)

Half Life of Teratogenic Agents in Different Animal Species

Agent	Mouse	Rat	Rabbit	Nonhuman primate	Human
Trimethadione	0.7	1.5-2.6	1-2		20-24
Valproic acid	0.8	0.3		0.7 – 3	12
Diazepam	1	1	3		20-50
13-cis retinoic acid	0.3	1			10-30
Cyclophosphamide	0.2	0.7		0.7	4
Caffeine	0.7	0.8	1.6	3.2	4.2


Plasma level
Peak concentration
Distribution
Absorption
Elimination
" AUC "
Time after Dose

Species Variation in the Metabolism of Amphetamines*

Species	Relative extent of metabolic pathway			
	Aromatic hydroxylation	N-Dealkylation	Deamination	Excreted unchanged
Rat	++++	+++	+	++
Guinea pig	-	++	++++	++
Rabbit	+	++	++++	+
Marmoset monkey	+		+	++++
Rhesus monkey	+++		+++	++
Human	++	+	+++	+++

*Nau (1989).

Pattern of Drug Metabolism in Various Animal Species as Models for the Human

	Similarity to the human in drug metabolism			
Animal species	**Good**	**Fair**	**Poor**	**Invalid**
Rat	**29%**	**12%**	**20%**	**42%**
Dog, rabbit, guinea pig	**32%**	**27%**	**9%**	**32%**
Rhesus monkey	**73%**	**19%**	**4%**	**4%**

Nau (1986).

Evaluation of Reproductive Risks based on Laboratory Studies

1. Is the reproductive toxicity observed in two or more species?

2. Are the reproductive effects tested in appropriate animal species?

3. Are specific effects (phenotypes) induced by the agent concerned?

4. Are the reproductive effects dose-related?

5. Is the embryotoxic dose far below the maternal toxicity dose?

6. What are the embryotoxic threshold dose and the NOAEL?

7. What is the difference between the embryotoxic dose in laboratory animals and the human clinical dose?

8. How serious could the possible effects be in humans?

9. What kind of human populations could be at risk?

Proof of Teratogenesis in the Human

1. Majority of epidemiological studies demonstrate an increased incidence of a particular group of malformations in exposed populations.

2. The incidence of patients prenatally exposed to the agent is significantly higher in the population having the particular group of malformations.

3. An animal model is developed which mimics the human situation.

4. The embryotoxic effects are dose-related.

5. The critical period and mechanism of teratogenesis are biologically plausible.

Modeified after Shepard (1994).

doi:10.1111/j.1741-4520.2009.00239.x Congenital Anomalies 2009; 49, 123–246 123

TERMINOLOGY

Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

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[1]US Environmental Protection Agency, Washington, DC; [2]GlaxoSmithKline, King of Prussia, Pennsylvania, USA; [3]Ruth Clark Associates, North Lincolnshire, UK; [4]Kyoto University, Kyoto, Japan; [5]Sanofi Aventis R&D, Vitry-sur-Seine Cedex, France; [6]Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany; [7]National Institute of Health Sciences, Tokyo; [8]Astellas Pharma, Osaka, Japan; [9]Charité University Medical School, Berlin, Germany; [10]MedImmune, Cambridge, UK; [11]Takeda Global Research and Development, Lake Forest, Illinois, USA; [12]Chiba Institute of Science, Chiba; [13]Sin Nippon Biomedical Laboratories, Kagoshima, Japan; [14]GlaxoSmithKline Services, Hertfordshire, UK; and [15]Merck Research Laboratories, West Point, Pennsylvania, USA

ABSTRACT **This update (Version 2) of the *Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 1)* incorporates improvements and enhancements to both content and organization of the terminology to enable greater flexibility in its application, while maintaining a consistent approach to the description of findings. The revisions are the result of an international collaboration among interested organizations, advised by individual experts and the outcomes of several workshops. The terminology remains organized into tables under the broad categories of external, visceral, and skeletal observations, following the manner in which data are typically collected and recorded in developmental toxicity studies. This arrangement of the tables, as well as other information provided in appendices, is intended to facilitate the process of specimen evaluation at the laboratory bench level. Only the commonly used laboratory mammals (i.e. rats, mice, rabbits) are addressed in the current terminology tables. The inclusion of other species that are used in developmental toxicity testing, such as primates, is considered outside the scope of the present update. Similarly, categorization of findings as, for example, 'malformation' or 'variation' remains unaddressed, in accordance with the overall principle that the focus of this document is descriptive terminology and not diagnosis or interpretation. The skeletal terms have been augmented to accommodate cartilage findings.**

Key Words: developmental toxicology glossary, developmental toxicology nomenclature, developmental toxicology terminology, external abnormality, skeletal abnormality, visceral abnormality

Correspondence: Susan Makris M.S., US Environmental Protection Agency (USEPA), Office of Research and Development, National Center for Environmental Assessment, Mail Code: 8623P, 1200 Pennsylvania Avenue, NW, Washington, DC 20460-0001, USA. Email: makris.susan@epa.gov

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Disclaimer: The views expressed in this document are those of the authors and do not necessarily reflect the views or policies of the US Environmental Protection Agency.

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*Teratology Society (USA).

†European Teratology Society.

‡Japanese Teratology Society.

§Appointed chair or co-chair of respective Teratology Society working group.

INTRODUCTION

This publication is the first update (i.e. Version 2) to the *Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 1)* by Wise *et al.* (1997). It builds upon past efforts to assemble an internationally harmonized source of common nomenclature for use in describing observations of fetal and neonatal morphology. Improvements and enhancements to the content and organization of the Version 1 terminology are provided to enable a greater degree of flexibility in its application, while maintaining a consistent approach to the description of findings. The terminology should be of particular use for submissions of developmental toxicity data to regulatory agencies, while also having broader applicability in research.

Version 1 was compiled under the auspices of the International Federation of Teratology Societies (IFTS), which included member groups from North America, Europe, and Asia. It was based on a glossary previously published by the Middle Atlantic Reproduction and Teratology Association (MARTA) (Feuston *et al.* 1986). Additional input was provided by the Midwest Teratology Association (MTA) and the IFTS International Committee on Nomenclature, which included the Italian Nomenclature Working Group, the UK Foetal Pathology Terminology Group and the French Teratology Association Nomenclature Working Group. Following the publication by Wise *et al.* (1997), a Japanese translation of the terminology paper was also published (Horimoto *et al.* 1998).

Over time, laboratories and regulatory agencies have gained practical experience in the application and interpretation of the internationally harmonized terminology presented in Version 1. Additionally, several international terminology workshops were held in Berlin from 1998 to 2007, some of which have been summarized in the published literature (Chahoud *et al.* 1999; Solecki *et al.* 2001; 2003). An image-based atlas that can serve as an illustrative resource for the harmonized terminology has also been compiled (e.g. BfR 2005).

THE JAPANESE TERATOLOGY SOCIETY

Japanese

Congenital Anomalies — THE JAPANESE TERATOLOGY SOCIETY

Laboratory animal Congenital Anomaly Database

meetings

- 51th Annual Meeting
  Date： July 22-24, 2010
  Place： Sabo Kaikan Tokyo 2-7-5 Hirakawacho, Chiyoda-Ku, Tokyo, 102-0093, Japan
  Chairman： Fumiki Hirahara(Yokohama City Univ.)
  H P：http://www.macc.jp/51jts/index.html

Topics & Whats NEW

- 2011.3.1. The homepage was renewed.

Labolatory animal Congenital Anomaly Database - Top Page

BACK UMIN TOP TOP MENU

All the data are offered by THE JAPANESE TERATOLOGY SOCIETY

Japanese / English

Brief Description	
Display a list of registered observation	Search for observation by category(ex. External/Visceral/Skeletal)
Search	Search by a synonym, related term or definition etc.
Initial regstration (for an administrator)	Add as a new entry. This function is exclusively for an administrator.

問い合わせ先:日本先天異常学会事務局 jts@ac-square.co.jp

Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

- (•) External
- ( ) Visceral
- ( ) Skeletal

next

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Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

Earlier search condition	
External/Visceral/Skeketal	External

Check All Uncheck All

General Head / Neck Ear

Eye Face Limb (fore- or hind-)

Paw / Digit (fore- or hind-) Tail Trunk

Display a list of registered observation next

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Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

1 2
1-10 / 12

No	Id Number	Code Number	Region Organ Structure	Observation	Synonym or Related Trem	Definition	File
1	S002429	10002	General	General/Conjoined twins	Omphalosite	Monozygotic twins with variable incomplete separation into two during cleavage or early stages of embryogenesis	○
2	S002430	New	General	General/Distended abdomen		Abdomen appears larger than normal	--
3	S002435	10004	General	General/Subcutaneous hemorrhage	Petechia, Purpura, Ecchymosis, Hematoma	An accumulation of extravasated blood beneath the skin	--
4	S002431	New	General	Fetus or pup/neonate/Discolored	Skin discolored	Generalized or localized region of abnormal color (other than pale)	--
5	S002432	New	General	Fetus or pup/neonate/Large			--
6	S002433	New	General	Fetus or pup/neonate/Pale		Generalized absence of color when compared to a normal specimen	--
7	S002434	New	General	Fetus or pup/neonate/Small	Runt		--
8	S000003	10001	General	Subcutaneous edema/Generalized	Anasarca	An accumulation of interstitial fluid in subcutaneous connective tissue	○
9	S002428	10005	General	Subcutaneous edema/Localized		Localized accumulation of fluid	--
10	S002436	10003	General	Skin/Absent	Cutis aplasia	Localized region of no skin development	--

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Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10001
External/Visceral/Skeletal	External
Region/Organ/Structure	General
Observation	Subcutaneous edema/Generalized
Synonym or Related Term	Anasarca
Non-Preferred Term	
Definition	An accumulation of interstitial fluid in subcutaneous connective tissue
Note	
Registration date	2010/01/28
Updated date	2010/11/26

Image information		
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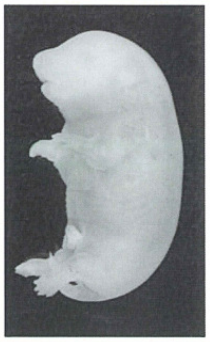
	memo	
	species	
	memo	

edit delete

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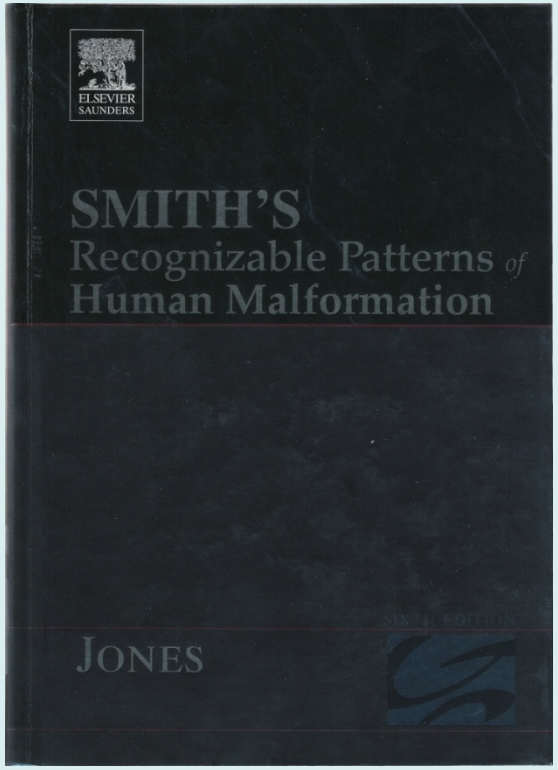
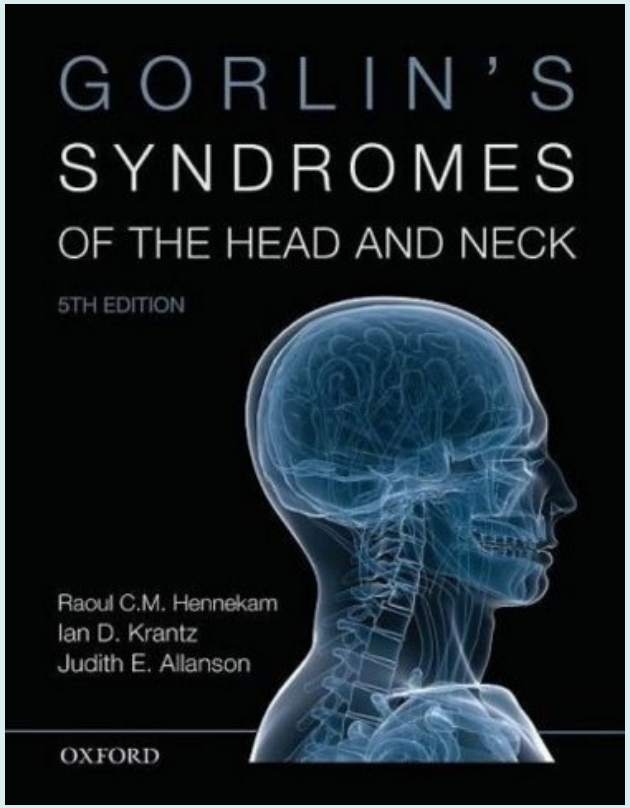
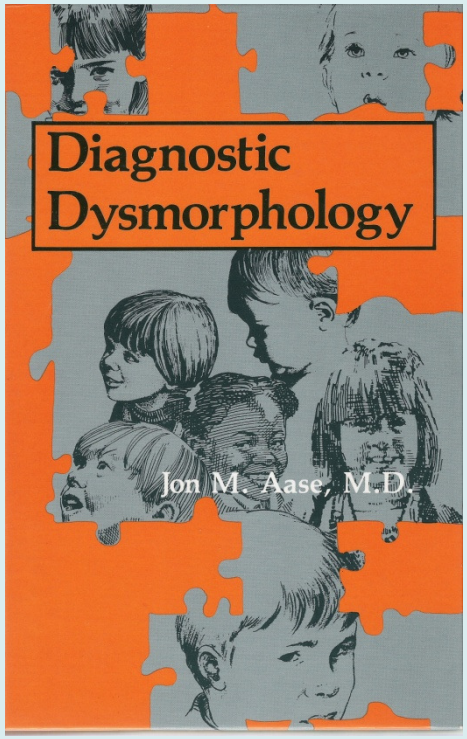
Selected books and atlases of human malformation (1)

1) SMITH'S Recognizable Patterns of Human Malformation (6th Ed): Kenneth L. Jones
2) Syndromes of the Head and Neck (5th Ed): Raoul C. M. Hennekam, Ian D. Krantz, Judith E. Allanson
3) Diagnostic Dysmorphology: Jon M. Aase

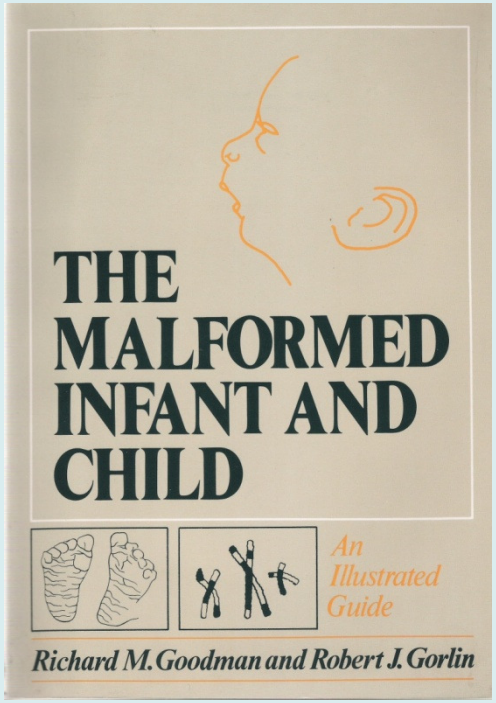


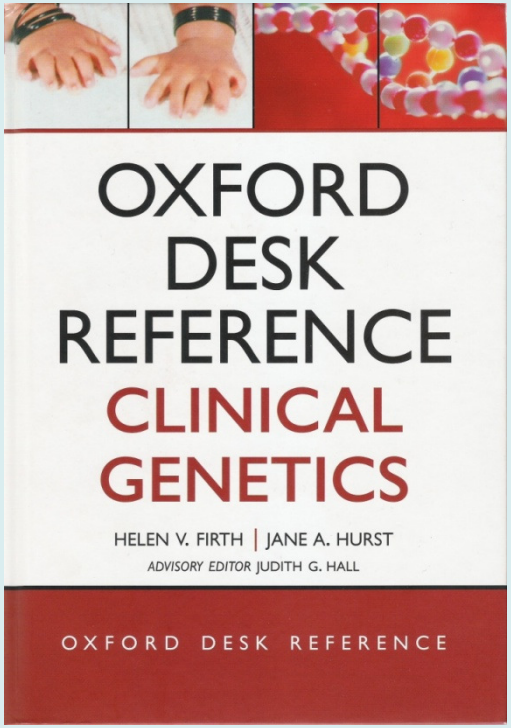


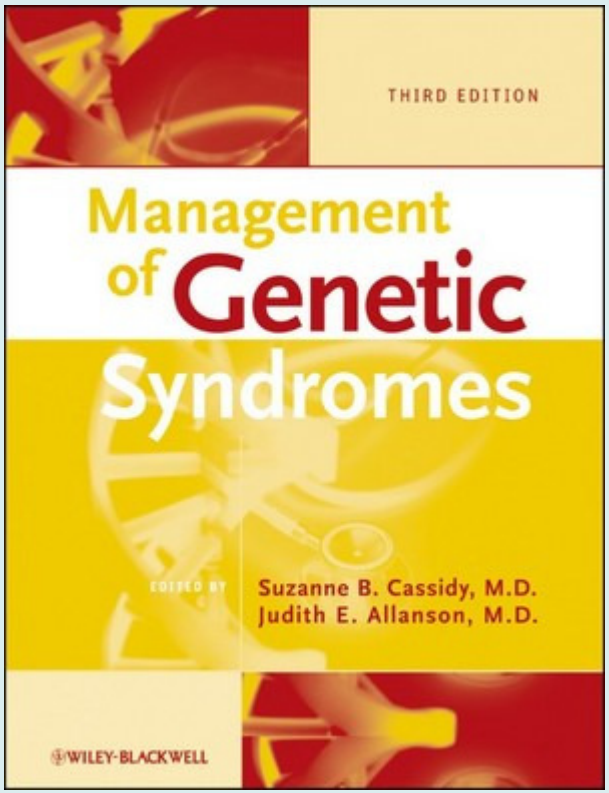


Selected books and atlases of human malformation (2)

4) The Malformed Infant and Child: Richard M. Goodman, Robert J. Gorlin
5) Oxford Desk Reference: Clinical Genetics: Helen V. Firth, Jane A. Hurst
6) Management of Genetic Syndromes (3rd Ed): Suzanne B. Cassidy, Judith E. Allanson

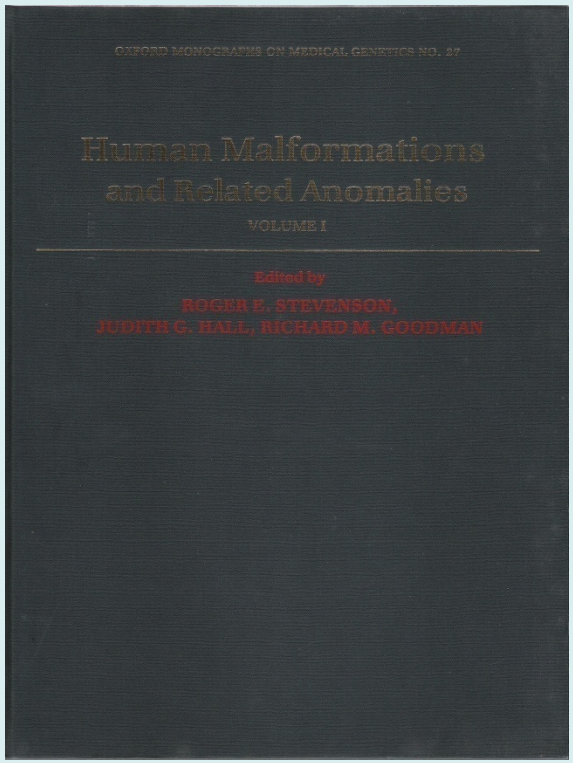


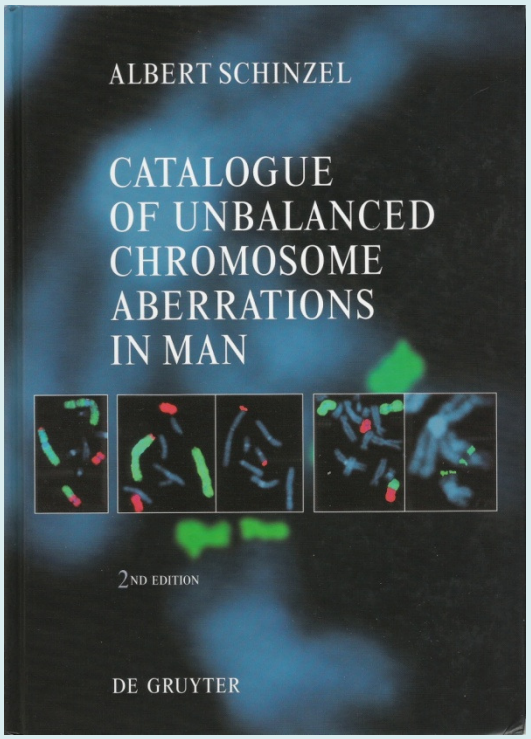


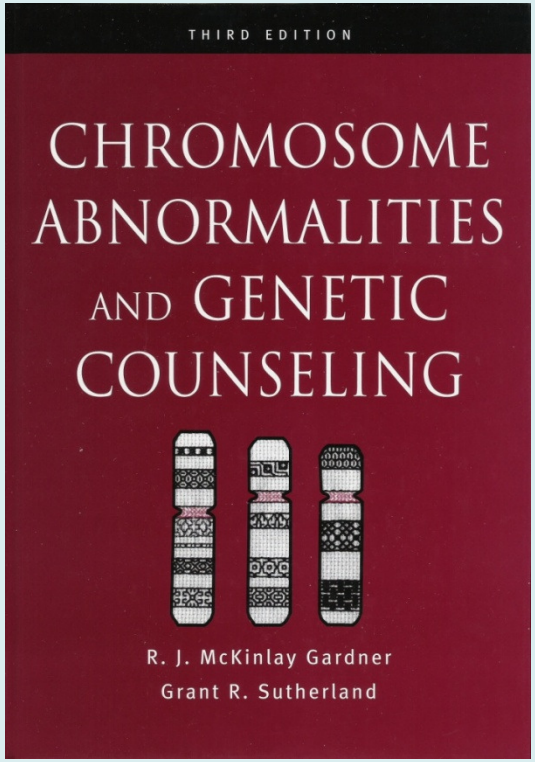


Selected books and atlases of human malformation (3)

7) Human Malformations and Related Anomalies Vol.1&2: Roger E. Stevenson, Judith G. Hall, Richard M. Goodman
8) Unbalanced Chromosome Aberrations in Man (2nd Ed): Albert Schinzel
9) Chromosome Abnormalities and Genetic Counseling (3rd Ed): R. J. McKinlay Gardner, Grant R. Sutherland

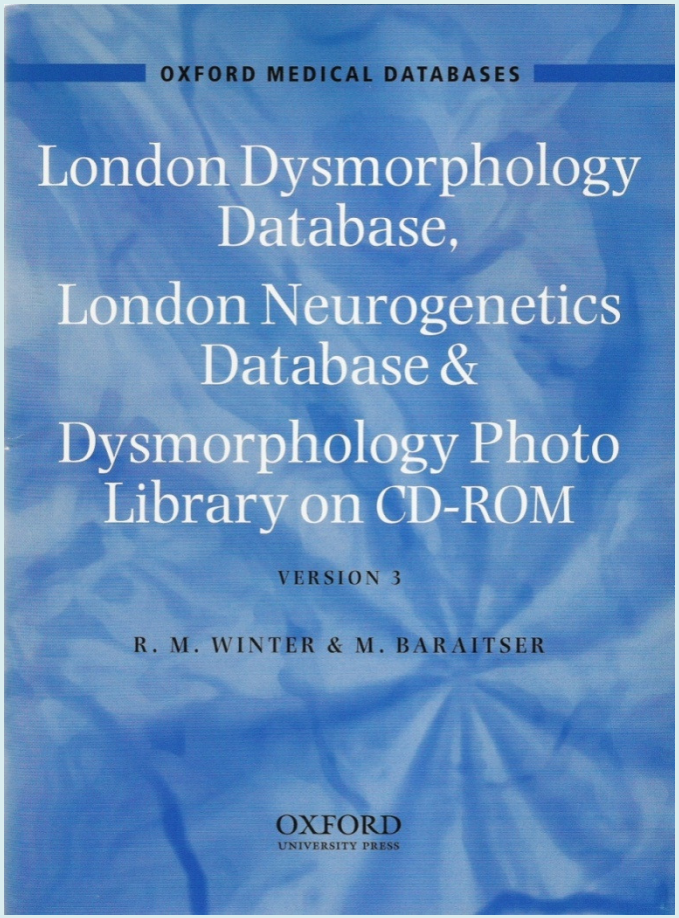


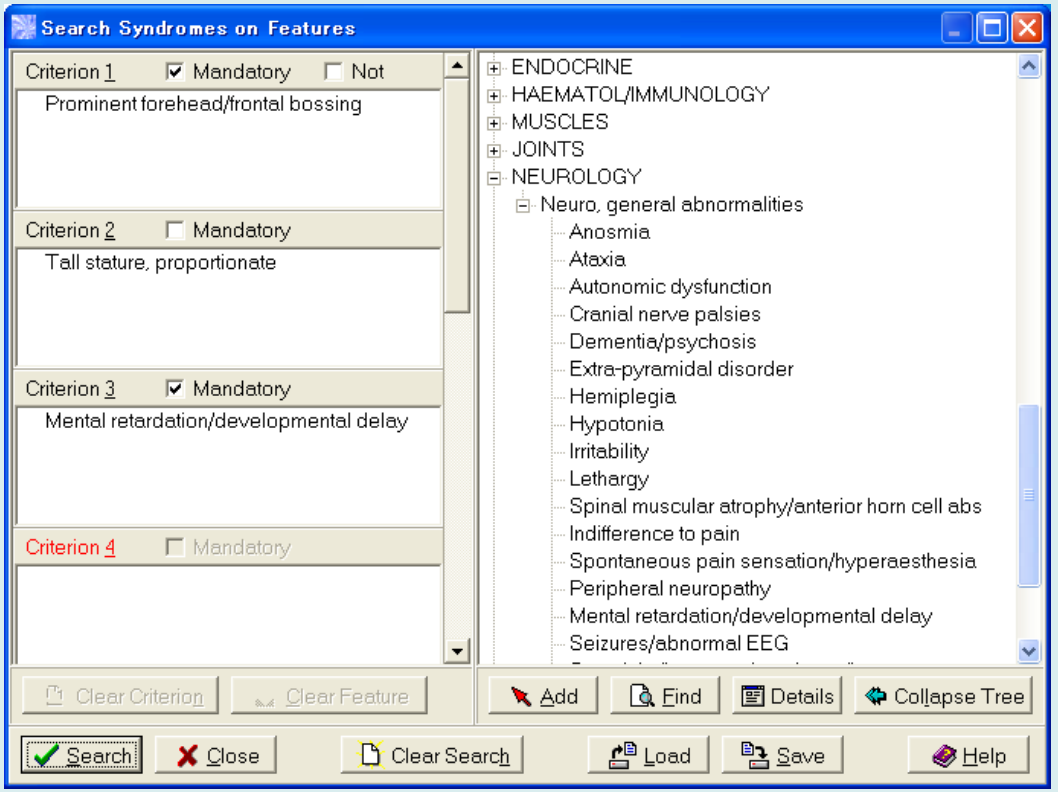




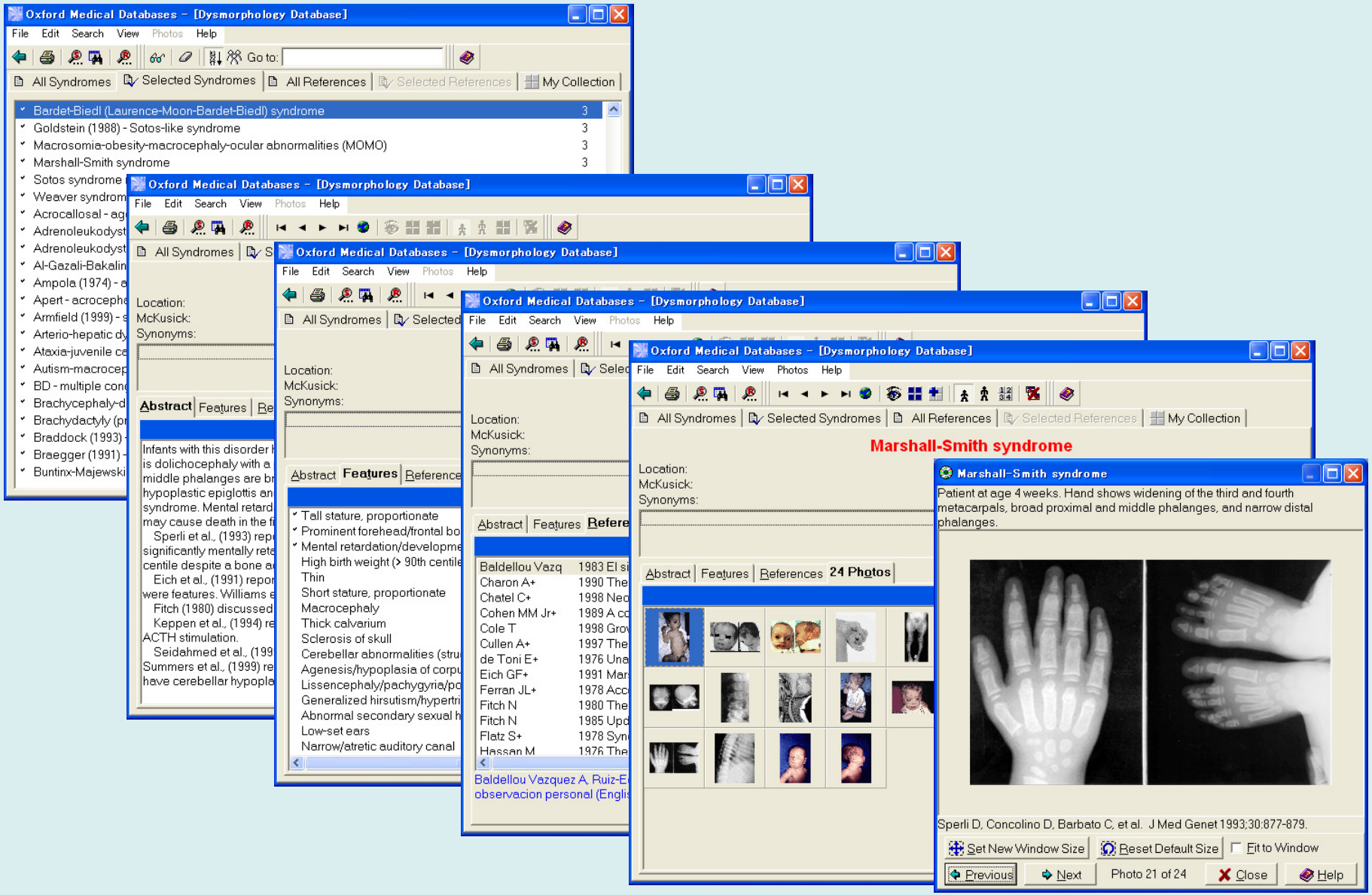
Databases of Human Malformation (1)

London Dysmorphology Database, London Neurogenetics Database & Dysmorphology Photo Library on CD-ROM: Oxford University Press 2001□□



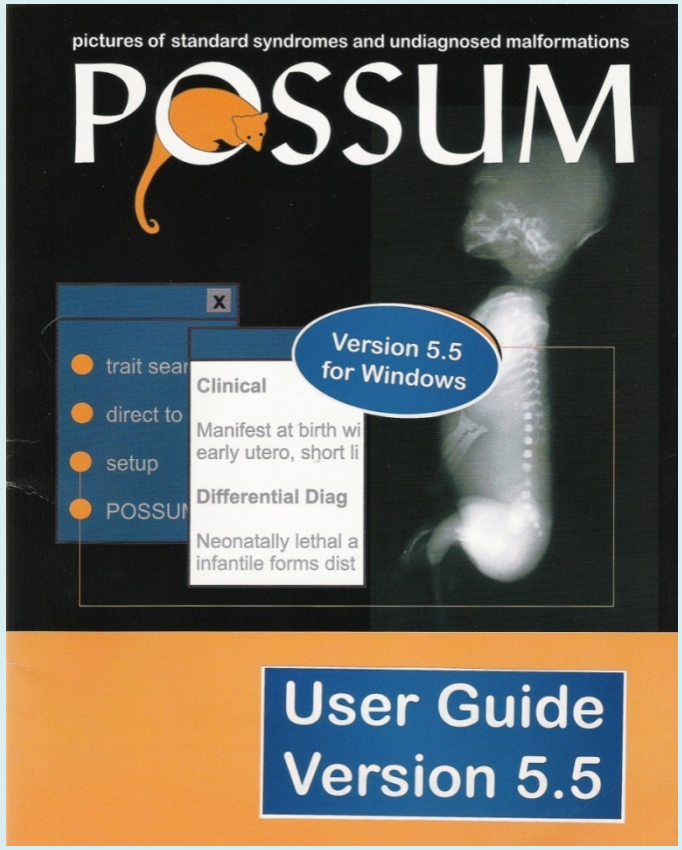


London Dysmorphology Database



Databases of Human Malformation (2)

Possum (Pictures of standard syndromes and undiagnosed malformations): The Murdoch Institute and the Telemedia Software Labs 2002□□



POSSUM

Pictures of Standard Syndromes and Undiagnosed Malformations

PAID

Hironao NUMABE

SALES INVOICE
Invoice No POSS001035
Customer Ref: fax#
Date: 14/02/02

DISK SIZE	DESCRIPTION	QUANTITY (USD)	BASE PRICE (USD)	NET PRICE (USD)
CD	Possum Version 5.5	1	2,000.00	2,000.00

Murdoch Childrens Research Institute

TAX RECEIPT

Received From
Hironao Numabe

Date of Issue: 15/02/2002

Receipt No: 0000001976

Being For

Description	Amount
POSS001035	3,835.83

Possum

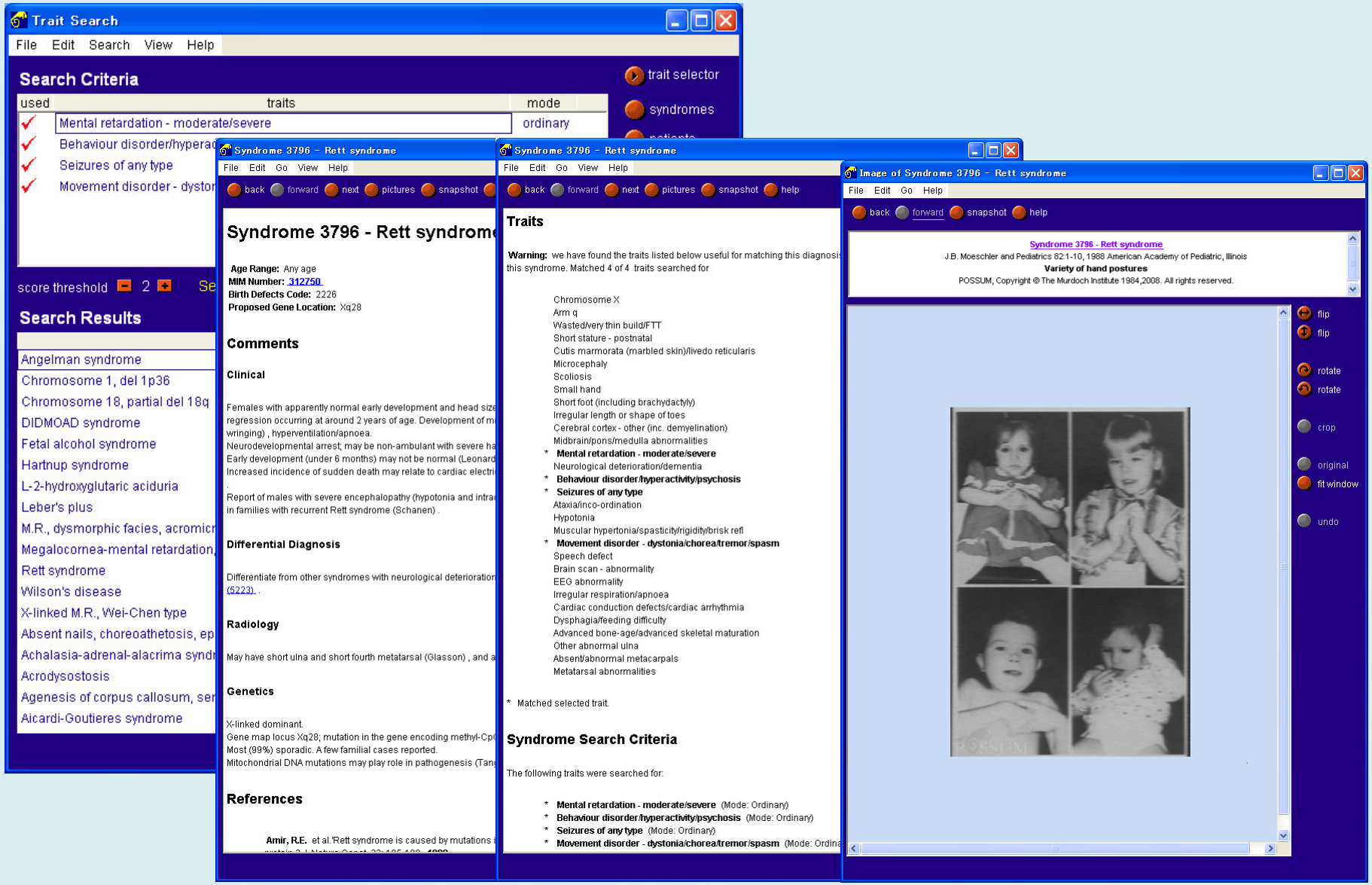

Trait Search
File Edit Search View Help
Search Criteria
trait selector
syndromes
used
traits
mode
Mental retardation - moderate/severe
ordinary
Behaviour disorder/hyperac
Seizures of any type
Movement disorder - dystor
score threshold 2
Search Results
Angelman syndrome
Chromosome 1, del 1p36
Chromosome 18, partial del 18q
DIDMOAD syndrome
Fetal alcohol syndrome
Hartnup syndrome
L-2-hydroxyglutaric aciduria
Leber's plus
M.R., dysmorphic facies, acromicr
Megalocornea-mental retardation,
Rett syndrome
Wilson's disease
X-linked M.R., Wei-Chen type
Absent nails, choreoathetosis, ep
Achalasia-adrenal-alacrima syndr
Acrodysostosis
Agenesis of corpus callosum, ser
Aicardi-Goutieres syndrome
Syndrome 3796 - Rett syndrome
File Edit Go View Help
back forward next pictures snapshot
Syndrome 3796 - Rett syndrom
Age Range: Any age
MIM Number: 312750
Birth Defects Code: 2226
Proposed Gene Location: Xq28
Comments
Clinical
Females with apparently normal early development and head size
regression occurring at around 2 years of age. Development of m
wringing) , hyperventilation/apnoea.
Neurodevelopmental arrest; may be non-ambulant with severe ha
Early development (under 6 months) may not be normal (Leonard
Increased incidence of sudden death may relate to cardiac electri
Report of males with severe encephalopathy (hypotonia and intra
in families with recurrent Rett syndrome (Schanen) .
Differential Diagnosis
Differentiate from other syndromes with neurological deterioration
(5223) .
Radiology
May have short ulna and short fourth metatarsal (Glasson) , and a
Genetics
X-linked dominant.
Gene map locus Xq28; mutation in the gene encoding methyl-Cp
Most (99%) sporadic. A few familial cases reported.
Mitochondrial DNA mutations may play role in pathogenesis (Tan
References
Amir, R.E. et al.'Rett syndrome is caused by mutations
Syndrome 3796 - Rett syndrome
File Edit Go View Help
back forward next pictures snapshot help
Traits
Warning: we have found the traits listed below useful for matching this diagnosi
this syndrome. Matched 4 of 4 traits searched for
Chromosome X
Arm q
Wasted/very thin build/FTT
Short stature - postnatal
Cutis marmorata (marbled skin)/livedo reticularis
Microcephaly
Scoliosis
Small hand
Short foot (including brachydactyly)
Irregular length or shape of toes
Cerebral cortex - other (inc. demyelination)
Midbrain/pons/medulla abnormalities
* Mental retardation - moderate/severe
Neurological deterioration/dementia
* Behaviour disorder/hyperactivity/psychosis
* Seizures of any type
Ataxia/inco-ordination
Hypotonia
Muscular hypertonia/spasticity/rigidity/brisk refl
* Movement disorder - dystonia/chorea/tremor/spasm
Speech defect
Brain scan - abnormality
EEG abnormality
Irregular respiration/apnoea
Cardiac conduction defects/cardiac arrhythmia
Dysphagia/feeding difficulty
Advanced bone-age/advanced skeletal maturation
Other abnormal ulna
Absent/abnormal metacarpals
Metatarsal abnormalities
* Matched selected trait.
Syndrome Search Criteria
The following traits were searched for:
* Mental retardation - moderate/severe (Mode: Ordinary)
* Behaviour disorder/hyperactivity/psychosis (Mode: Ordinary)
* Seizures of any type (Mode: Ordinary)
* Movement disorder - dystonia/chorea/tremor/spasm (Mode: Ordina
Image of Syndrome 3796 - Rett syndrome
File Edit Go Help
back forward snapshot help
Syndrome 3796 - Rett syndrome
J.B. Moeschler and Pediatrics 82:1-10, 1988 American Academy of Pediatric, Illinois
Variety of hand postures
POSSUM, Copyright © The Murdoch Institute 1984,2008. All rights reserved.
flip
flip
rotate
rotate
crop
original
fit window
undo
POSSUM

FIG. 1. Nomenclature group members present in November 2006 in Rome (Suzanne Cassidy was also present but could not be depicted on this picture). From left to the right are visible (first row) Helga Toriello, Cynthia Curry, Julie McGaughran, M Michael Cohen Jr, Louise Wilson, John Carey, Fiorella Gurrieri, Valerie Cormier-Daire, (second row) Jaime Frias, Giovanni Neri, Judith Allanson, Judith Hall, Karen Temple, Alain Verloes, (third row) Michael Patton, Alasdair Hunter, Gene Hoyme, Helen Hughes, John M Graham Jr, (fourth row) Roger Stevenson, Leslie Biesecker, Koen Devriendt, Bryan Hall, and Raoul Hennekam.

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

Elements of Morphology: Standard Terminology for the Head and Face

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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 introduce the anatomy of the craniofacies and define and illustrate the terms that describe the major characteristics of the cranium and face. Published 2009 Wiley-Liss, Inc.†

Key words: nomenclature; definitions; anatomy; anthropometry; head; cranium; face; neck; chin; maxilla; mandible

How to Cite this Article:
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Am J Med Genet Part A 149A:6–28.

INTRODUCTION

General

This paper is part of a series of six papers defining the morphology of regions of the human body [Biesecker et al., 2008; Carey et al., 2008; Hall et al., 2008; Hennekam et al., 2008; Hunter et al., 2008]. The series is accompanied by an introductory article describing general aspects of this study [Allanson et al., 2008]. The reader is encouraged to consult the introduction when using the definitions. The definitions are listed alphabetically based on the physical feature, not the modifier. When a feature is indicated in the text in ***Bold-italics***, a definition is available either in this paper or one of the accompanying papers.

The appearance of facial morphology varies considerably with facial expression and movement, and depending on the position of the observer and observed person. When assessing a feature, the head of the observed person should be held in the Frankfurt horizontal, with the facial and neck muscles relaxed, eyes open, lips making gentle contact, and facial expression neutral. The face of the observer should be at the same height as the face of the observed person.

Anatomy of the Face and Cranium

Head shape and upper face shape are closely related to the shape of the bony skull. Figures 1 and 2 show the bony anatomy of the face. Many anthropological landmarks, bony and soft tissue, are illustrated in Figures 3 and 4.

The Anatomy of the Various Structures is Described in More Detail Below.

Cranium: The upper part of the skull consists of paired frontal and parietal bones and a single posterior occipital bone (Figs. 1 and 2). In early life these bones are separated by five major sutures (Figs. 1 and 2). Three, the coronal, lambdoidal and squamosal, are paired, and two, the sagittal and metopic, are single. Cranial growth normally occurs perpendicular to each of these major sutures.

Forehead: The part of the face above the eyebrows, below the hairline and between the temples. The paired frontalis muscles join in the midline and adhere to the superficial fascia over the frontal bone. These muscles effect forehead wrinkling or furrowing. They have no bony attachments, but inferiorly the fibres blend with the

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DOI 10.1002/ajmg.a.32612

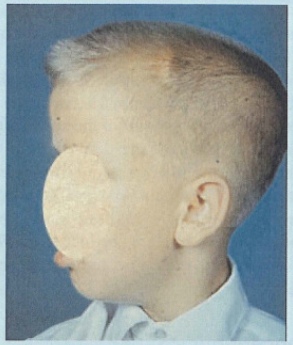


FIG. 7. *Macrocephaly*. Note the increased size of the cranium. Differences in size are difficult to appreciate but increased head size in this child is notable because of comparison with the smaller face.

Macrocephaly

Definition: Occipitofrontal (head) circumference greater than 97th centile compared to appropriate, age matched, sex-matched normal standards (Fig. 7). *objective* OR

Apparently increased size of the cranium. *subjective*

Comments: Head circumference is measured from just above the glabella (the most prominent point on the frontal bone above the root of the nose) to the most posterior prominent point of the occipital bone using a tape measure. Some standard charts are organized by centiles [Hall et al., 2007], others by standard deviations [Farkas, 1981]. It is important to add an indication of how far above the normal standard the head circumference is if an accurate assessment of this can be made. Macrocephaly is an absolute term. The term relative macrocephaly can be used when the head size centile exceeds the centile for height, for example, head size at the 75th centile with height at the 5th centile for age and sex.

Synonyms: Head circumference, enlarged; OFC, large.

Replaces: Macrocranium

Macrocranium: See ***Macrocephaly***

Microcephaly

Definition: Occipito-frontal (head) circumference (OFC) less than 3rd centile compared to appropriate, age matched, normal standards (Fig. 8). *objective* OR

Apparently decreased size of the cranium. *subjective*

Comments: Head circumference is measured from just above the glabella (the most prominent point on the frontal bone above the root of the nose) to the most posterior prominent point of the occipital bone using a tape measure. Some standard charts are organized by centiles [Hall et al., 2007], others by standard deviations [Farkas, 1981]. It is important to add an indication of how far below the normal standard the head circumference is if an accurate assessment of this can be made. Microcephaly is an absolute term. The term relative microcephaly can be used wh the head size centile is less than the centile for height, for examp head size at the 3rd centile with height at the 75% for age and s

Synonyms: Head circumference, reduced small; OFC, small.

Replaces: Microcranium

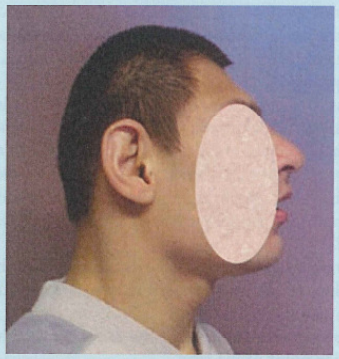


FIG. 8. *Microcephaly*. Decreased size of the cranium is accompanied by marked posterior sloping of the forehead.

Microcranium: See ***Microcephaly***

Occiput, Flat

Definition: Reduced convexity of the occiput (posterior part skull) (Fig. 9). *subjective*

Comments: Reduced convexity of the occiput gives an appe ance of flattening. There are no objective measures for convexity the occiput, and evaluation depends heavily on the experience of t observer. This finding may or may not be accompanied ***Brachycephaly*** (which should be coded separately), and may observed more frequently when an infant is placed to sleep on h her back.

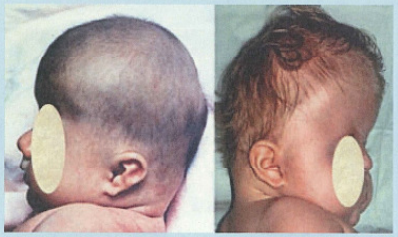


FIG. 9. *Occiput, flat*. There is reduced convexity of the occiput giving an appearance of flattening of the back of the skull.

Oligodontia

Comment: The term is not defined here since the finding requires a radiograph, as is true for anodontia and for the other designation of tooth agenesis, hypodontia. The terms hypodontia and oligodontia are sometimes used interchangeably in the literature while on other occasions hypodontia is used for selective agenesis of six or less missing teeth while oligodontia is applied when there are more than six missing teeth. Tooth agenesis or oligodontia/hypodontia can be mistaken for delayed eruption and again a radiograph is needed for diagnosis. Absence of teeth may be congenital (tooth agenesis) or acquired. The incidence of congenital absence of teeth is different depending on the type and position of the tooth [Gorlin et al., 2001].

Open Bite

Definition: Visible space between the dental arches in occlusion (Fig. 37). *objective*

Comments: An open bite produces an absence of vertical overlap of the two dental arches. It may be associated with malocclusion, but this should be coded separately. Open bite can be accompanied by malocclusion, which is a complex bundled term. The Angle classification of malocclusion (Classes I–III) is widely used in the orthodontics community [Moyers, 1973] for the characterization of malocclusion.

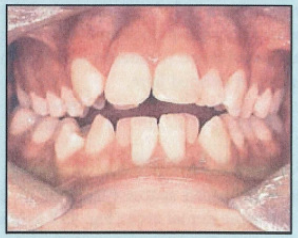


FIG. 37. *Open bite*. Note the space between the dental arches. (Figure courtesy of Duane Yamashiro.)

Palate, Hard, Short

Definition: Distance between the labial point of the incisive papilla to the midline junction of the hard and soft palate more than 2 SD below the mean (Fig. 38). *objective*

or apparently decreased length of the hard palate. *subjective*

Comment: Objective measurement of the hard palate requires special instrumentation [Hall et al., 2006]. A short hard palate may be associated with velopharyngeal incompetence.

Replaces: Short palate; hypoplastic palate

Palate, short: see ***Palate, hard, short***

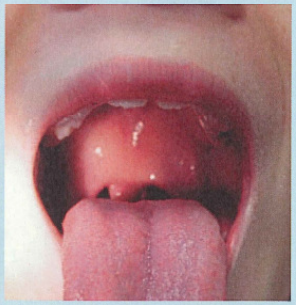


FIG. 38. *Short hard palate*. (Figure courtesy of Alan Rope.)

Palate, High

Definition: Height of the palate more than 2 SD above the mea *objective* OR

Palatal height at the level of the first permanent molar more th twice the height of the teeth (Fig. 39). *subjective*

Comments: The measuring device for this assessment is d scribed in Hall et al. [2006]. A high palate is often associated witl narrow palate. However, a narrow palate can easily give a fa appearance of a high palate. Height and width of the palate shou be assessed and coded separately. We do not recommend t subjective determination because this term can be overused a applied inaccurately.

Synonym: High, arched palate

Palate, high arched: see ***Palate, high***

Palate, hypoplastic: see ***Palate, hard, short***

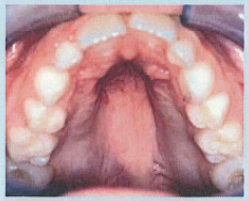


FIG. 39. *High palate*. Note a Narrow palate is a different feature and can produce the false appearance of a high palate.

Palate, Narrow

Definition: Width of the palate more than 2 SD below the mea *objective*

OR apparently decreased palatal width (Fig. 40). *subjective*

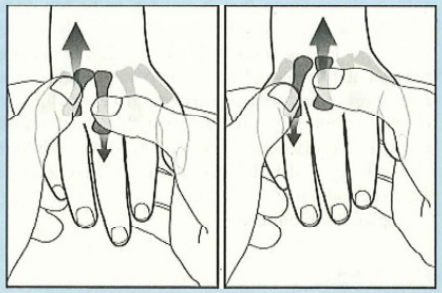


FIG. 38. *Osseous syndactyly of the hand.* This figure shows the maneuver used to detect this finding. The abnormal finding is not shown. The examiner grasps two adjacent metacarpals and alternately moves them to determine if they are fused or independent.

Hand, Postaxial Polydactyly of

Definition: Presence of a supernumerary digit that is not a thumb (Fig. 39). *objective*

Comment: Although it is appealing to believe in many cases that the supernumerary (non-thumb) digit is the most ulnar, there may be no evidence for this. When the digit is *de minimus*, this seer reasonable by parsimony. When it is fully formed with a supern merary metacarpal and functional, it may be impossible to det mine which of the fingers is supernumerary. Nevertheless, t designation as postaxial is reasonable given the tradition of tl designation. Postaxial polydactyly has been divided into two typ A (a fully formed digit) and B (*digitus minimus*, or a pedunculate non-articulating, non-functional appendage). We recognize the subtypes but note that post-axial polydactyly actually represent spectrum from type A to type B. When the type is indeterminate, subtype is specified.

Synonym: Posterior polydactyly

Replaces: Ulnar polydactyly; Posterior duplication of the lim hand

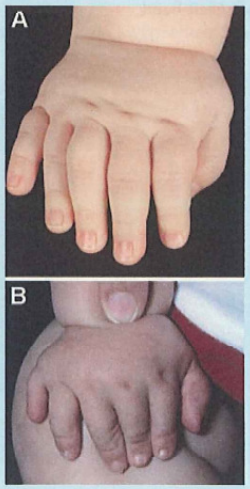


FIG. 39. A: *Postaxial polydactyly of the right hand, type A.* B: *Postaxial polydactyly of the right hand.* Note that this patient has a digit that is intermediate between type A and type B, so that is not specified. See also Figures 49A, 58A, and 73A. See Figures 9A and 11A for examples of *Postaxial polydactyly, type B.*

Hand, Preaxial Polydactyly of

Definition: Duplication of all or part of the first ray (Fig. 4(*objective*

Comment: There is a wide spectrum of this malformation. T mild end of the spectrum is a bifid (not cleft) nail or a distal phala of the thumb with a central lacuna or bifid tip. Broadened thum

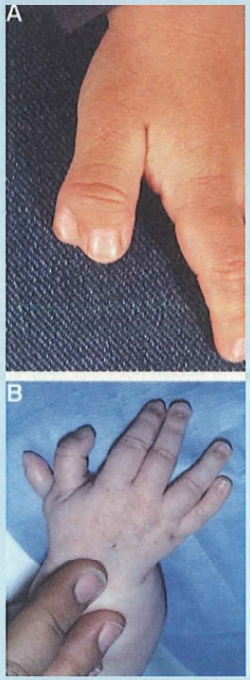


FIG. 40. A: *Preaxial polydactyly of the left hand, partial.* B: *Preaxial polydactyly of the right hand.*

Problems in making comparative databases for laboratory animals and humans

1. Clinical terms are mainly diagnostic terms.

   (Ex. Polydactyly, spina bifida, holoprosencephaly).

2. “Privacy” of the patient is an obstacle when publishing human clinical cases.


I'd feel a little more secure if some of the scientists were pregnant....

The frequency, type and severity of induced malfomations depend on the following conditions.

1. **Developmental stage of embryos/fetuses when they are exposed to teratogenic agents.**
2. **Dosage of the agent**
3. **Teratogenic threshold**
4. **Genotype of the embryo/fetus (species and strain difference)**
5. **Placental transfer**
   Rate and extent
6. **Drug metabolism in the maternal-fetal unit**

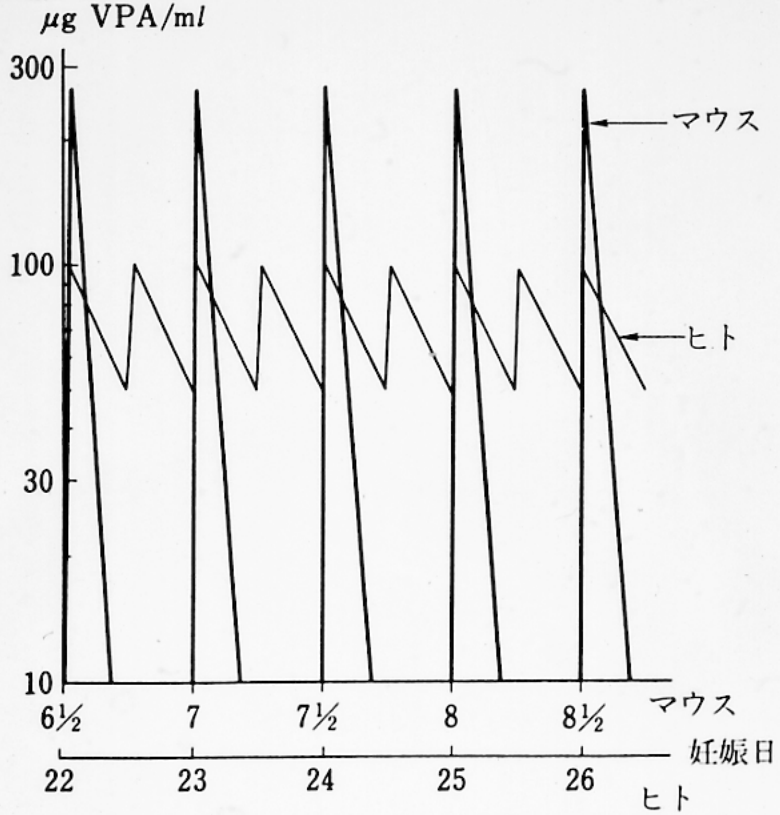
For better assessment of embryotoxicity/teratogenicity of exogenous agents

- Well-designed laboratory studies
  - Precise description of observed results
- Proper data analysis
- Extrapolation to the human
- Assessment of human risk

- Knowledge on normal and abnormal development
- Data on pharmacokinetics and drug metabolism

PARAMETERS DETERMINING THE RATE AND EXTENT OF DRUG TRANSFER TO THE EMBRYO

Drug transfer	Parameters
Rate	Lipid solubility of drugs[a]
	Molecular weight of drugs[a]
	Placental blood flow
	Placental structure and function
	Active transport of drugs
Extent	pKa of the drug
	Maternal/embryonic pH gradient (cf. Chapter 5)
	Protein binding of drugs
	Active transport of drugs



マウスで外脳症を10％誘発する投与条件（1日2回投与）の血中濃度をヒトの臨床例におけるそれと対比してある

図2.4.3　マウスとヒトにおけるバルプロ酸の血中濃度の比較

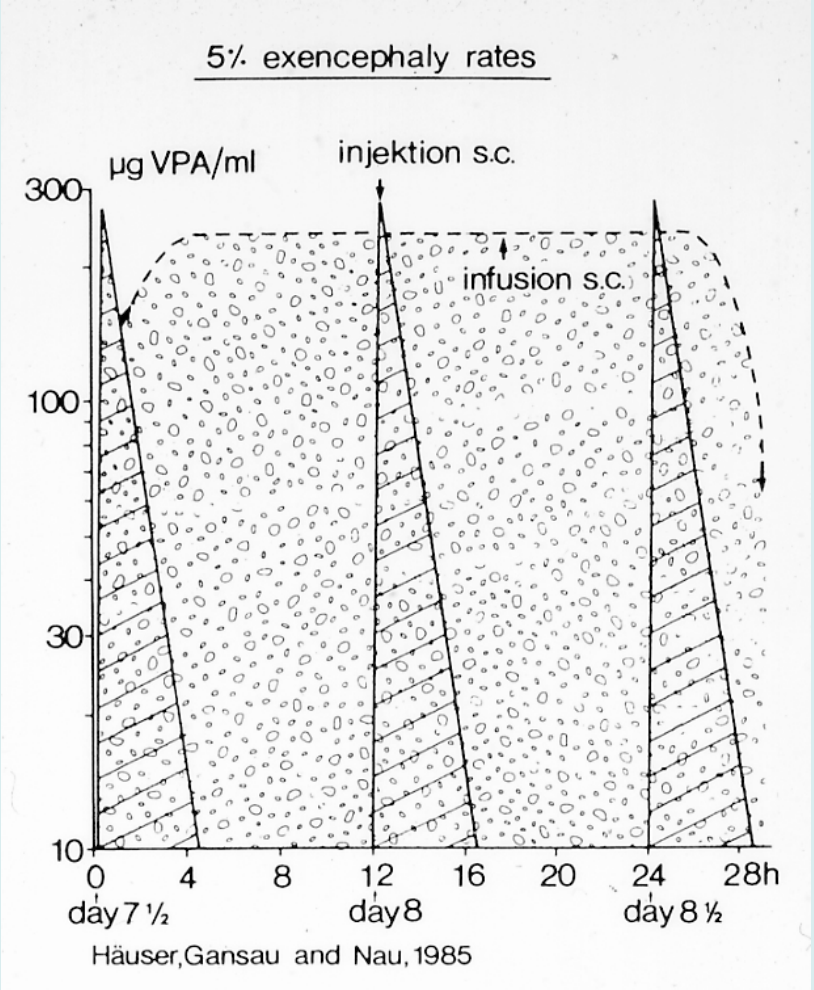
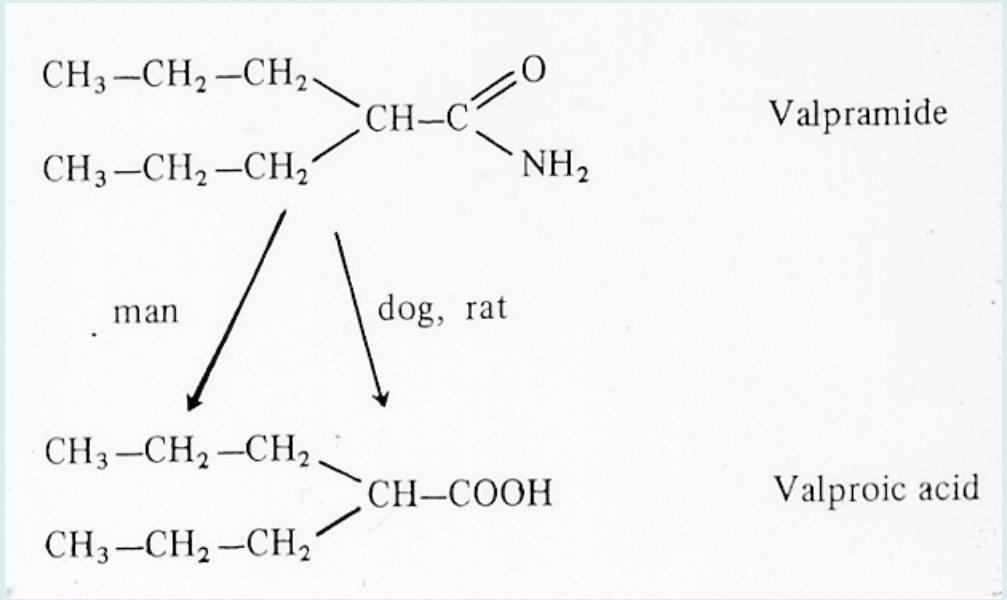


表 2.4.4　各動物種におけるバルプロ酸の催奇形作用とたん白結合[23,24]

動物種	催奇形性			たん白結合 (%)	半減期 (時間)
	神経管奇形	顔面奇形	骨格奇形		
マウス	＋＋＋	＋	＋＋＋	30～50	0.8
ラット	—	—	＋＋＋	60～80	0.3～1
ハムスター	＋			50～60	1
ウサギ	—	—	＋＋	80～90	1
サル	—	＋	＋＋	80	0.7～3.5
ヒト	＋	＋	＋	85～95	9～18

—：催奇形作用なし，＋，＋＋，＋＋＋：相対的な催奇形作用の強さを表わす．



SPECIES DIFFERENCES OF VPA TERATOGENICITY

Species	Effects			
	Neural tube	Orofacial	Skelet.	Ref.
Mouse	+ + +	+	+ + +	9—12
Rat	–	–	+ + +	13, 14
Hamster	+	?	?	15
Rabbit	–	–	+ +	16
Monkey	–	+	+ +	17, 18
Man	+	+	+	19—24

発生毒性の評価

1．その毒性は２種類以上の動物種で見られているか．
2．その外因に特異的な異常が誘発されるか．
3．発生毒性は親動物に対する毒性よりもかなり低い用量で起こっているか．
4．その毒性には用量一効果関係が見られるか．
5．用量一効果関係の傾斜はどれほどか．
6．発生毒性試験が最も適切な動物種においてヒトでの適用経路を用いて行われているか．
7．発生毒性の閾値と無影響量（NOEL）はどれほどか．
8．発生毒性用量とヒトの臨床用量との間にどれほどの差があるか．
9．その異常がヒトに起こった場合に生命や生体機能に重大な障害を及ぼすか．
10．どのような集団がリスクを受ける可能性があるか．

[illegible]

1. [illegible]safety factor[illegible]
2. [illegible]LD_{50} / [illegible]
3. [illegible] / [illegible]
4. [illegible] / [illegible]
5. [illegible]NOEL[illegible]/ [illegible]
6. [illegible] / [illegible]

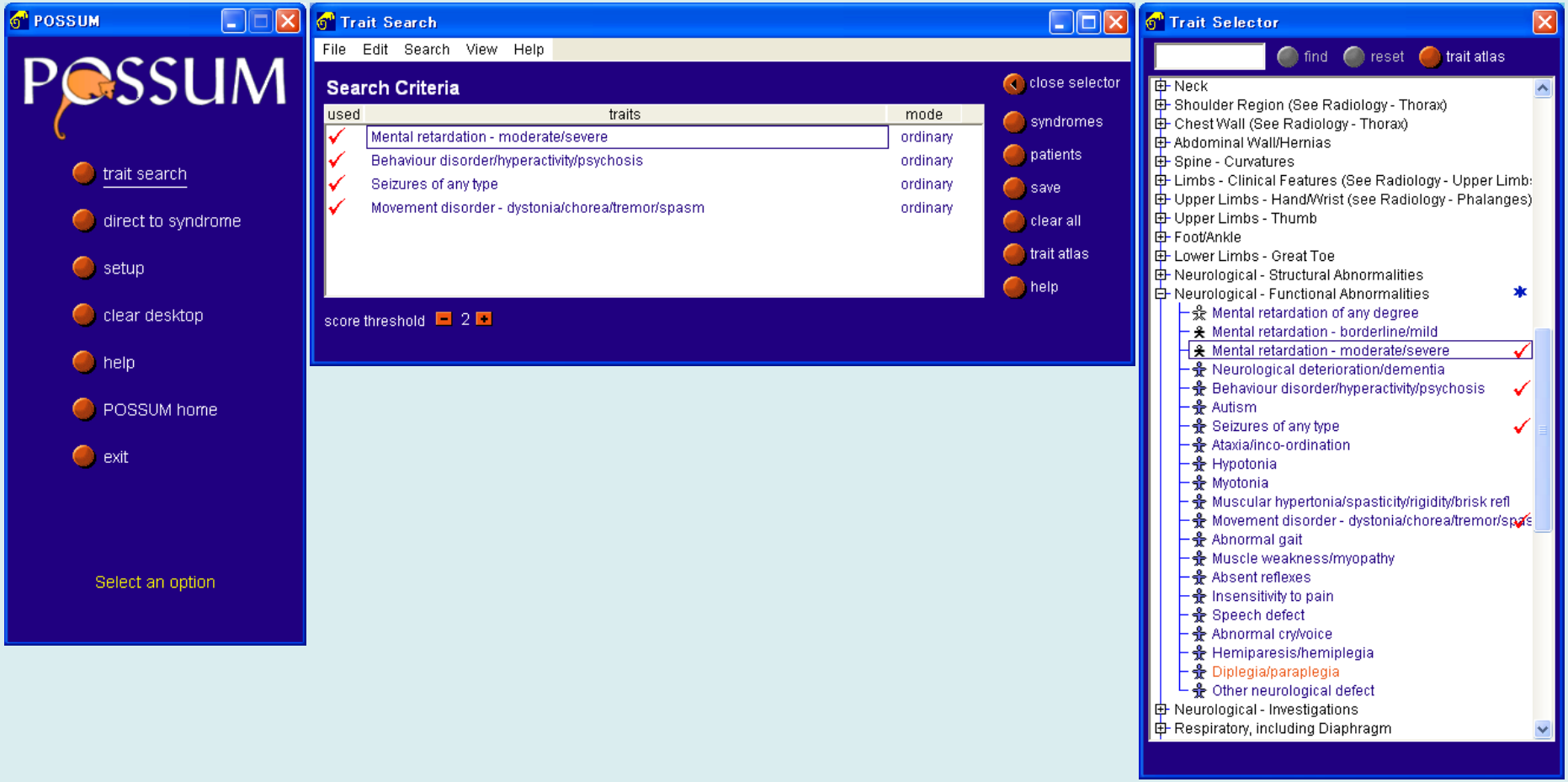
   [illegible] (A/D) [illegible]

   [illegible]

   [illegible]LD_{01}/tD_{05}[illegible]

   [illegible]

Possum


POSSUM
POSSUM
trait search
direct to syndrome
setup
clear desktop
help
POSSUM home
exit
Select an option
Trait Search
File Edit Search View Help
Search Criteria
used
traits
mode
Mental retardation - moderate/severe
ordinary
Behaviour disorder/hyperactivity/psychosis
ordinary
Seizures of any type
ordinary
Movement disorder - dystonia/chorea/tremor/spasm
ordinary
close selector
syndromes
patients
save
clear all
trait atlas
help
score threshold 2
Trait Selector
find
reset
trait atlas
Neck
Shoulder Region (See Radiology - Thorax)
Chest Wall (See Radiology - Thorax)
Abdominal Wall/Hernias
Spine - Curvatures
Limbs - Clinical Features (See Radiology - Upper Limb
Upper Limbs - Hand/Wrist (see Radiology - Phalanges)
Upper Limbs - Thumb
Foot/Ankle
Lower Limbs - Great Toe
Neurological - Structural Abnormalities
Neurological - Functional Abnormalities
Mental retardation of any degree
Mental retardation - borderline/mild
Mental retardation - moderate/severe
Neurological deterioration/dementia
Behaviour disorder/hyperactivity/psychosis
Autism
Seizures of any type
Ataxia/inco-ordination
Hypotonia
Myotonia
Muscular hypertonia/spasticity/rigidity/brisk refl
Movement disorder - dystonia/chorea/tremor/spas
Abnormal gait
Muscle weakness/myopathy
Absent reflexes
Insensitivity to pain
Speech defect
Abnormal cry/voice
Hemiparesis/hemiplegia
Diplegia/paraplegia
Other neurological defect
Neurological - Investigations
Respiratory, including Diaphragm

UR-DBMS

UR-DBMS
(University of the Ryukyus-Database for Malformation Syndromes)

Syndrome Finder

※医師専用(利用希望者はユーザ登録をお願いします。)

UR-DBMSは琉球大学医学部医科遺伝学(遺伝医学)により作成された奇形症候群を中心とする遺伝性疾患の総合データベースです。ご利用の際は**UR-DBMS**ボタンをクリックして、検索画面へお進みください。

Syndrome Finderは症状や所見から診断を推定することができます。医師専用ですので、利用の際にはユーザ登録が必要です。**Syndrome Finder**ボタンをクリックして、ログイン画面へお進みください。

URDBMSについて

http://becomerich.lab.u-ryukyu.ac.jp/

□□□□□□□□□□
□□□□□□□□□

1) OMIM
   http://www.ncbi.nlm.nih.gov/omim
2) GeneReviews
   http://www.geneclinics.org/
3) GeneReviews Japan
   http://grj.umin.jp/
4) Genetic Alliance
   http://www.geneticalliance.org/
5) Genetics Home Reference
   http://ghr.nlm.nih.gov/
6) Chromosomal Variation in Man
   http://www.wiley.com/borgaonkar/
7) Chromosome Deletion Outreach, Inc.
   http://www.chromodisorder.org/

Proof of Teratogenesis

1. Majority of epidemiological studies demonstrate an increased incidence of a particular group of malformations in exposed populations.

2. The incidence of patients prenatally exposed to the agent is significantly higher in the population having the particular group of malformations.

3. Rare environmental exposure associated with rare defects. Probably three or more cases.

4. An animal model is developed which mimics the human situation.

5. The embryotoxic effects are dose-related.

6. The critical period and mechanism of teratogenesis are biologically plausible.

Modified after Shepard (1998).

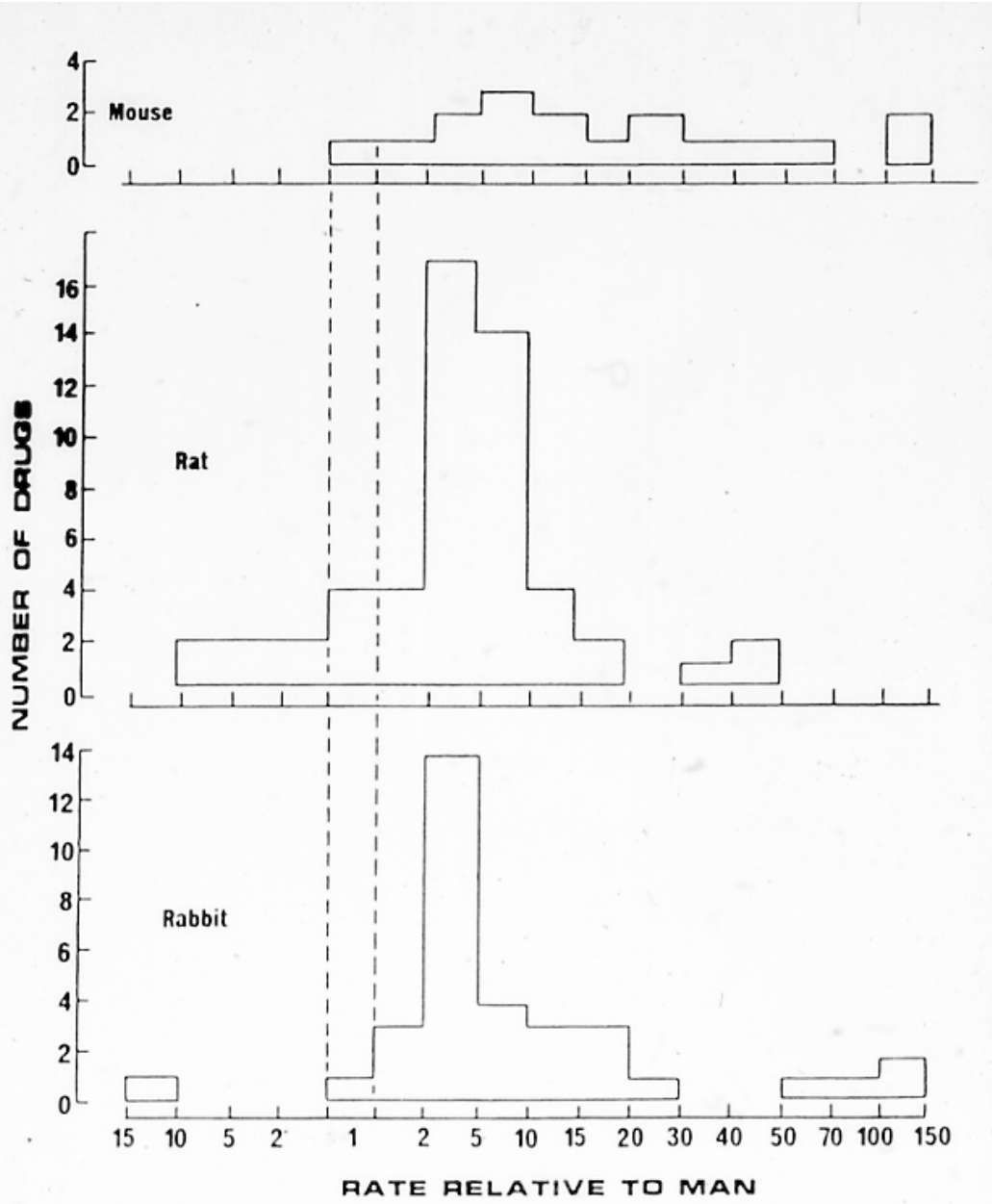


FIGURE 4. Clearance of drugs (normalized for body weight by mouse, rat, and rabbit compared to man. The figures represent the number of drugs cleared at rates expressed relative to man. Drugs cleared at identical rates appear as 1. Drugs to the left of this value are cleared at rates lower than man, drugs to the right are cleared at rates greater than man.

Labolatory animal Congenital Anomaly Database - Observation List

BACK UMIN TOP TOP MENU

1 2
1-10 / 17

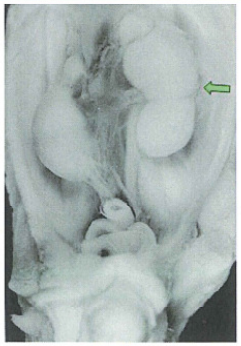
No	Id Number	Code Number	Region Organ Structure		Observation	Synonym or Related Trem	Definition	File
1	S002909	10328	Kidney	Kidney	Cyst			--
2	S002911	10331	Kidney	Kidney	Large			--
3	S002914	10337	Kidney	Kidney	Misshapen			○
4	S002915	10339	Kidney	Kidney	Small			--
5	S002907	10326	Kidney	Kidney	Absent			○
6	S002910	10330	Kidney	Kidney	Discolored	Infarct		--
7	S002913	10336	Kidney	Kidney	Malpositioned			--
8	S002912	10332	Kidney	Kidney	Fused			--
9	S002916	10342	Kidney	Kidney	Supernumerary			--
10	S002908	New	Kidney	Kidney	Altered texture			--

問い合わせ先:日本先天異常学会事務局 jts@ac-square.co.jp

Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10337
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Kidney
	Kidney
Observation	Misshapen
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	
Registration date	2010/04/19
Updated date	2011/03/03

Image information		
	species	rat
	memo	

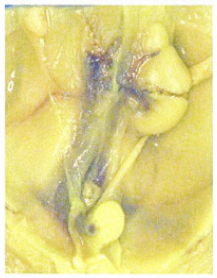
edit delete

問い合わせ先：日本先天異常学会事務局 jts@ac-square.co.jp

Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10326
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Kidney
	Kidney
Observation	Absent
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	
Registration date	2010/04/19
Updated date	2011/03/03

Image information		
	species	dog
	memo	
	species	rat
	memo	

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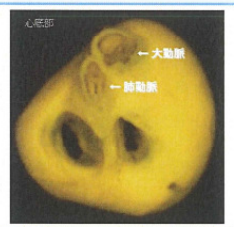
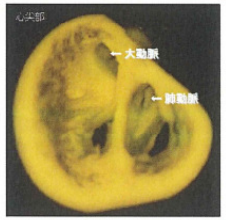
Labolatory animal Congenital Anomaly Database - Details

BACK UMIN TOP TOP MENU

Observation information	
Code Number	10224
External/Visceral/Skeletal	Visceral
Region/Organ/Structure	Great vessels
	Great vessels
Observation	Transposition
Synonym or Related Term	
Non-Preferred Term	
Definition	Origin of aorta from right ventricle and pulmonary trunk from left ventricle
Note	
Registration date	2011/03/03
Updated date	2011/03/03

Image information		
	species	rat
	memo	
	species	rat
	memo	

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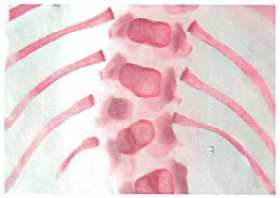
問い合わせ先:日本先天異常学会事務局 jts@ac-square.co.jp

Labolatory animal Congenital Anomaly Database - Details

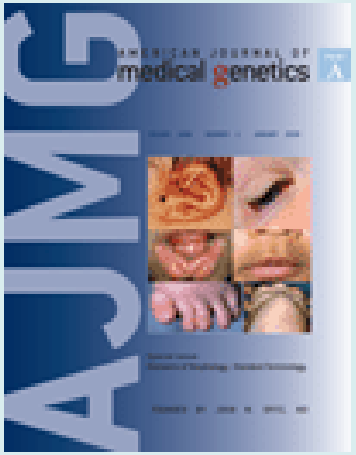
BACK UMIN TOP TOP MENU

Observation information	
Code Number	10696
External/Visceral/Skeletal	Skeletal
Region/Organ/Structure	Vertebra
	Thoracic vertebra
Observation	Hemivertebra
Synonym or Related Term	
Non-Preferred Term	
Definition	
Note	Absent arch and hemicentrum may be recorded separately
Registration date	2010/04/19
Updated date	2011/03/04

Image information		
	species	rabbit
	memo	

edit delete

問い合わせ先:日本先天異常学会事務局 jts@ac-square.co.jp



American Journal of Medical Genetics

Special Issue: Elements of Morphology: Standard Terminology

January 2009

Volume 149A, Issue 1

Pages 1–127

Editorial comment: Editor's foreword to a special issue “Elements of Morphology: Standard Terminology” (page 1)John C. Carey

Elements of morphology: Introduction (pages 2–5)Judith E. Allanson, Leslie G. Biesecker, John C. Carey and Raoul C.M. Hennekam

Elements of morphology: Standard terminology for the head and face (pages 6–28)Judith E. Allanson, Christopher Cunniff, H. Eugene Hoyme, Julie McGaughran, Max Muenke and Giovanni Neri

Elements of morphology: Standard terminology for the periorbital region (pages 29–39)Bryan D. Hall, John M. Graham Jr., Suzanne B. Cassidy and John M. Opitz

Elements of morphology: Standard terminology for the ear (pages 40–60)Alasdair Hunter, Jaime L. Frias, Gabriele Gillessen-Kaesbach, Helen Hughes, Kenneth Lyons Jones and Louise Wilson

Elements of morphology: Standard terminology for the nose and philtrum (pages 61–76)Raoul C.M. Hennekam, Valerie Cormier-Daire, Judith G. Hall, Károly Méhes, Michael Patton and Roger E. Stevenson

Elements of morphology: Standard terminology for the lips, mouth, and oral region (pages 77–92)John C. Carey, M. Michael Cohen Jr., Cynthia J.R. Curry, Koenraad Devriendt, Lewis B. Holmes and Alain Verloes

Elements of morphology: Standard terminology for the hands and feet (pages 93–127)Leslie G. Biesecker, Jon M. Aase, Carol Clericuzio, Fiorella Gurrieri, I. Karen Temple and Helga Toriello