CATALOG OF TERATOGENIC AGENTS

Second Edition

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INTRODUCTION

Defects existing at birth, irrespective of their cause, create societal problems of such magnitude that the subject needs little amplification. Approximately 3% of all human newborns have a congenital anomaly requiring medical attention, and approximately one-third of these conditions can be regarded as life threatening. With increasing age, over twice as many congenital defects are detected. Close to one-half the number of children in hospital wards are there because of prenatally acquired malformations of one kind or another.

Our knowledge about the cause and prevention of these problems is extremely limited. About 10 percent are associated with gene mutations and another 5% with chromosomal aberrations. Less than 3% of the remaining anomalies are known to be due to a teratogenic agent. Although there are over 600 agents listed in this catalog that can produce congenital anomalies in experimental animals, only about twenty of these are known to cause defects in the human. Therefore, there exists a wide difference between our knowledge of experimental teratology and the role that external agents play in producing human malformations.

A further problem is that the teratologic literature is dispersed throughout most of the biomedical publications rather than being confined to one or two of the specialized journals. Although a number of excellent review articles have been published, a catalog such as this has not been available. Harold Kalter's (1) text deals with the teratology of the central nervous system in animals, and Josef Warkany's (2) extensive treatise is concerned with congenital defects in man. David Smith's (3) popular book on dysmorphic syndromes helps to define and extend our description of human defects. McKusick's (4) catalog of mendelian inheritance in man includes over 300 congenital syndromes produced by gene mutations.

The main purpose of this catalog is to help link the information on experimental teratogenic agents with the congenital defects in man. The catalog should provide a source of reference for teratologists wishing knowledge of the literature dealing with a particular teratogenic agent. For the obstetrician, pediatrician, and geneticist it should help answer the often-asked question: Does this agent produce congenital defects in man or animal? Another function of this book may be to aid the scientists who protect us from our man-modified environment. Testing pharmaceutical products has become a major responsibility, and the environmental protectionist is also faced with the safety of food additives and household products. This catalog also may be useful to chemists working to develop new products. Unfortunately, because of species variability, at least in part, in teratogenic sensitivity, the ultimate testing of some products has been done in the human, with the alert clinician acting as monitor.

Comparative Time Periods of Embryonic and Fetal Development in Man and Experimental Animals

DEVELOPMENTAL EVENT	MAN	SPECIES-AGE (DAYS)*						
		MONKEY	RAT	MOUSE	RABBIT	HAMSTER	GUINEA PIG	CHICK
Total Gestational Time	267	166	21-22	18-20	31-34	15.5-16	64-68	20-21
Blastula	4-6	4-9	3-5	3-6	2.6-6	3-4.5	4.8	
◦ Implantation	6-7	9	5-6	7	6	4.5-5	6	
⁘ Primitive Streak	16-18	18-20	9	8	6.5	7	13.5	0.25-0.75
△ Neural Plate	18-20	19-21	9.5	8		7.5	13.5	1
□ First Somite	20-21	20-21	10	8.3-		7.7 -	14.5	1
□ Branchial Arch, First	20		10	8.3		7.75	15.5 -	1.5
Heart-First Beats	22		10.2			8. -	16.5 -	1.5 -
Pronephros	22		10				16.5	1.5
Oral Plate Perforation	24		10	9.1		8.5		2.75
◦ Anterior Neuropore Closed	24-25	23-24?	10.5	9	9.5	8.25	15.5	2.3 -
◦ Mesonephros	25		11-12	9.5		9	16.5	1.75
◦ Otocyst Closed	25		11.3	9		8.5	16.5 +	2.3 -
10 Somites	25-26	23-24	10.5	8.6	9 -	8	15.5	1.5
Three Branchial Arches	26		11.5	9.6		8.25	16.5	2.3
◊ Mesonephric Duct to Cloaca	26		12	11			18.5	3
Thyroid Appears	27		10	8.5			16.5	1.8
Upper Limb Bud	27-28	25-26	10.5	9.3	10.5	8.25	16.5	2.2
Posterior Neuropore Closed	26-27		11.3	9.5		8.5	16.5?	3.75
Fetuses Per Litter (Number)	1	1	8-10	12-13	6-9	10-14	2-3	
References-Number (see pp. xvi – xvii)	3, 10, 13, 17, 19, 24 27	11	2, 5, 12, 16, 17, 18 29	4, 8, 20	4, 5	1, 6, 23	22	9, 17

Comparative Time Periods of Embryonic and Fetal Development in Man and Experimental Animals

DEVELOPMENTAL EVENT	SPECIES-AGE (DAYS)*						
	MAN	MONKEY	RAT	MOUSE	RABBIT	HAMSTER	GUINEA PIG	CHICK
20 Somites	27-28	26	11.3	9.2	10-	8.5	16.5	2
Metanephric Bud Appears	28		12.3				19.1	4
Lung Bud Appears	28		12.1	9.6		9	17.5	3
Crown-Rump Length, 5 mm	29-30	26	13	10.5	11			
• Lower Limb Bud Appears	29-30	26-27	11.2?	10.3	11	9.75	18.5	2.5
Spiral Septum Begins	34		11.5			10		4.5
Herniation of Gut	34		12.5	12.3	14.5		23.7	19-20
Eye Pigment	34-35			11.3	14			3
⁘ Digital Rays-Upper Extremity	35	84	13.4	12.3	14.5	10.25	23.7	4.75
Crown-Rump Length, 10 mm	37	33	15	13.5	14			
⁘ Ossification Begins	40-43		17-18	12.5		12.5		8
Müllerian Duct Appears	40		13.5			11	23.7-	4
Cloaca Divided by Urorectal Septum	43		17					
Δ Testes, Histological Differentiation	43		14.5		20	12	26.1	5.5
Digit Separation	43-47			15.3			28 -	8.5
Heart Septation Complete	46-47		15.5	13		11	26.1	8 -
◦ Eye Lids Closed	56-58	53 -	18	16.3 +	20 -	13.5		13
◊ Palate Closed Completely	56-58	44-45	16-17	15	19-20	12.25		
Herniation of Gut Reduced	60		18	16.3 -				
Urethral Groove Closed in Male	90							
References-Number (see pp. xvi - xvii)	3, 10, 13, 17, 19, 24-27	11	2, 5, 12, 16, 17, 18, 29	4, 8, 20	4, 5	1, 6, 23	22	9, 17

It is important that the presently accumulated information on teratogens be fully utilized to recognize potential teratogenic hazards and to prevent congenital malformations in man. If it happens that many anomalies are produced by the interaction of genes with a teratogenic agent, it undoubtedly will be easier to remove the agent than to alter the action of the gene. The work of producing this book will be rewarded if it contributes to the prevention of any congenital defects.

The teratogenic agents listed in this book include chemicals, drugs, physical factors, and viruses. I have attempted to make a complete listing of all agents that can produce congenital defects in animals or humans. The chemical names are, in most cases, those that appear in the *Merck Index*, but cross-indexing to alternate chemical and proprietary names has been done also. Studies carried out on species phylogenetically below the chick have been omitted. No attempt has been made to list agents that are teratogenic only when administered in combination with another agent. I have not attempted a critical exclusion of agents that are doubtful teratogens. *The presence of an agent in the catalog does not necessarily indicate that it is a teratogen* because a number of compounds, often considered teratogenic but with substantially negative teratogenic effects, have been included. When there is conflicting evidence of teratogenicity, equal representation has been attempted. An example of this is lysergic acid diethylamide (LSD).

The literature has been surveyed using the usual library aids. When possible, abstracts of work have not been utilized. Numerous excellent references dealing only with the mechanism of the defects' production have been omitted. Although some agents may have been omitted inadvertently from this listing, the method of production and printing of this type of book readily allows for easy revision. I hope that scientists in the field will feel free to send me new information or corrections for inclusion in future editions, and to encourage this, an addressed form has been included in the final pages of this book.

Each listing includes a main entry with synonyms. This is followed by a brief account of some of the work published including species, dose, gestational age at time of administration, and type of congenital defects produced. The references following each entry were chosen because of their review nature, originality, or because they are most current.

During the early planning of the book it appeared that the accumulation of the new teratologic literature could very rapidly outdate a text published in the usual manner. To obviate this partially, the catalog was constructed using a computerized system. The phrase *computerized system* has puzzled some of my associates, who initially concluded that I used some mechanical device for generating information. On the contrary, the text was compiled in the usual way and then transferred to computer cards. This text was then stored on computer tape, from which a printout could be obtained. This computerized system for producing a catalog allows for easy insertion of new material or corrections during compilation and for easy production of future editions. It has the further advantage that, with the use of photocopying, the book can be printed in less than 3 months at a considerably reduced cost.

Since a teratogenic agent is defined by its ability to produce a congenital defect, it seems appropriate to provide a definition for "congenital defect" at this point. A congenital defect has its genesis during embryonic or fetal development and consists of a major or minor deviation from normal morphology or function. The border line between a minor congenital defect and normal variation is most difficult to define, and this accounts for a large difference in incidence rates. David Smith (3) has offered some criteria for distinguishing the two. In general, a minor defect

should be present in less than 2% or 3% of the population. This small percentage could be defined in a statistical manner as the number of observations falling outside of three standard deviations from the mean. Large morphological types of congenital defects such as cleft palate or meningomyelocele may be called anomalies or malformations, but I feel the term *defect* also includes unknown or subtle structural defects that alter function. These functional changes also could be ascribed to molecular changes, many of which are still unknown. Particularly in the nervous and endocrine systems, changes in postnatal function have become an important aspect of both experimental and human teratology. An example of this is maternal hyperphenylalaninemia, which may lead to cerebral dysfunction and mental retardation in the offspring. Another new and important teratologic area requiring long term postnatal observation is prenatally induced oncogenesis, illustrated by vaginal carcinomas produced in grown girls whose mothers were treated with diethylstilbesterol during pregnancy.

A teratogenic agent acts during pregnancy to produce a physical or functional defect in the conceptus or offspring. The definition can be made more specific by using a modification of Koch's postulates in the following manner:

Koch's postulates	*Application to Teratology*
1. A specific microorganism must be present in each case.	1. The agent must be present during the critical periods of development.
2. A pure culture of the organism should produce a similar disease in the experimental animal.	2. The agent should produce congenital defects in an experimental animal. The defect rate should be statistically higher in the treated group than in the control animals receiving the same vehicle or sham procedure.
3. Organisms from the experimental animal must be recovered and grown in pure culture.	3. Proof should be obtained that the agent in an unaltered state acts on the embryo-fetus either directly or indirectly through the placenta. In this area, biochemistry and organ culture are most often used instead of bacteriology.

The fulfillment of the first two conditions is sufficient to define a teratogenic agent. The third may be considered desirable but not essential. In this catalog, there are few teratogens that fit all three of these criteria. Surprisingly, teratogenic agents in the human generally do fill all three criteria—for instance, rubella virus, radiation, and androgens that masculinize the female fetus. Thalidomide, although accepted universally as a teratogen, does not fit the third criterion because the compound in its unaltered state has not been demonstrated to directly affect the conceptus. Although this third criterion may seem unnecessary to many teratologists, I believe that a more complete knowledge of these important molecular mechanisms can generate more rapidly the means for preventing malformations.

Several difficult problems face the teratologist in judging whether an agent is a teratogen. When the dosage level of a compound must be raised to near-fatal levels for the mother before defects are produced in her fetus, most workers consider the agent weakly teratogenic. However, clinicians, the Federal Drug Administration,

and the pharmaceutical industry encounter difficult decisions in applying these experimental findings to man. Agents causing embryonic or fetal death in experimental animals often later prove to be teratogenic in man but are not considered to be teratogens unless physical or functional defects are produced. Similarly, an agent that can cause fetal growth retardation does not necessarily qualify as a teratogen. Retardation of fetal skeletal maturation reported as decreased ossification centers of the manubrium or immaturity of the vertebral centra is another example of a change considered physiologic but not teratogenic.

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00027 ALCOHOL, ALCOHOLISM [ETHANOL]

SANDOR (1968) INJECTED THE EQUIVALENT OF 0.3 ML OF ETHANOL INTO THE CHICK AIR SAC AT 23 HOURS OF INCUBATION AND PRODUCED NEURAL TUBE AND CEREBRAL VESICLE DEFORMITIES ALONG WITH SOME MESODERMAL DEFECTS. SANDOR AND AMELS (1971) INJECTED PREGNANT RATS INTRAVENOUSLY AT 6 AND 7 DAYS OF GESTATION WITH 1.0 TO 2.0 GM OF ETHANOL PER KG AND FOUND EMBRYOLETHALITY BUT NO DEFECTS IN THE SURVIVING FETUSES. CHERNOFF (1975) IN A PRELIMINARY REPORT FED PREGNANT MICE BEFORE AND DURING PREGNANCY WITH A METRACAL DIET CONTAINING 15 TO 30 PERCENT ETHANOL DERIVED CALORIES. AT THE HIGHER CONCENTRATIONS RESORPTIONS OCCURRED FREQUENTLY. NEURAL TUBE CLOSURE DEFECTS AND CARDIAC MALFORMATIONS WERE FOUND IN A SIGNIFICANT NUMBER OF OFFSPRING.

A FETAL ALCOHOL OR ALCOHOLISM SYNDROME HAS BEEN DELINEATED IN THE HUMAN. JONES ET AL (1973) DESCRIBED 8 CHILDREN FROM MOTHERS WITH CHRONIC ALCOHOLISM. THE CHILDREN WERE CHARACTERIZED BY SMALL BIRTH WEIGHT, MICROCEPHALY, REDUCTION IN WIDTH OF THE PALPEBRAL FISSURES AND MAXILLARY HYPOPLASIA. FIVE HAD CARDIAC ANOMALIES. IN A SUBSEQUENT REPORT JONES AND SMITH (1973) ESTIMATED THAT ABOUT ONE-THIRD OF THE OFFSPRING OF CHRONIC ALCOHOLIC MOTHERS HAD THE SYNDROME. TWO OF THEIR CHILDREN HAD CLEFT PALATES. ALL OF THE INFANTS HAD SOME FORM OF DEVELOPMENTAL DELAY (JONES ET AL, 1974). ONE AUTOPSY REPORT SHOWING MALORIENTATION OF THE BRAIN HAS APPEARED (JONES AND SMITH, 1975). LEMOINE ET AL (1968) IN A PREVIOUSLY OBSCURE PAPER DESCRIBED 127 CHILDREN FROM ALCOHOLIC MOTHERS AND FOUND A VERY SIMILAR CLINICAL PICTURE WITH A 25 PERCENT MALFORMATION RATE WHICH INCLUDED IN PARTICULAR CLEFT PALATE AND CARDIAC ANOMALIES. OTHER REPORTS OF THE SYNDROME HAVE APPEARED (PALMER ET AL, 1974; FERRIER ET AL, 1973; MANZKE AND GROSSE, 1975).

THE HUMAN SYNDROME MAY NOT BE DUE PRIMARILY TO ALCOHOL AND OTHER FACTORS SUCH AS POOR PROTEIN INTAKE, PYRIDOXINE OR OTHER B VITAMIN DEFICIENCY, ALCOHOL CONTAMINANTS SUCH AS LEAD OR GENETIC PREDISPOSTTION MAY PLAY AN IMPORTANT ETIOLOGIC ROLE.

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