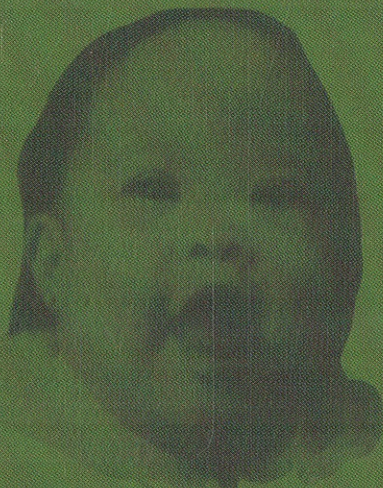
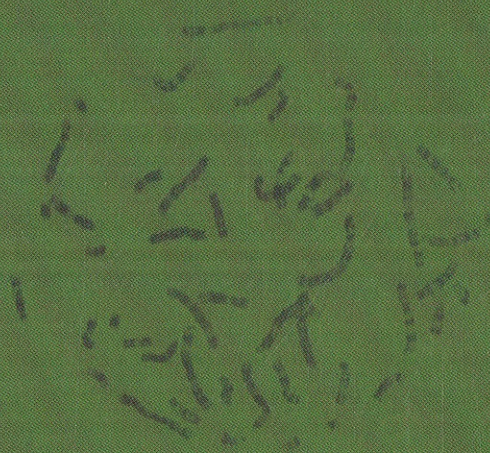


# The Consequences of Chromosome Imbalance

Principles, Mechanisms,  
and Models

Charles J. Epstein



# Contents

<i>Preface</i>	page	xiii
<i>Glossary</i>		xvii

## PART I: INTRODUCTION

1. The problem of aneuploidy	3
The human impact of aneuploidy	3
Causation	6
Approach to understanding the mechanisms of the deleterious effects of aneuploidy	6
Organization of the book	8

## PART II: CLINICAL OBSERVATIONS

2. The differentiability and variability of phenotypes	13
Differentiability	14
Variability	15
3. The partitioning of phenotypes	22
Double aneuploidy	22
<i>Whole chromosomes</i>	22
<i>Chromosome segments</i>	23
<i>Combined segmental aneuploidy of single chromosomes</i>	33
<i>Inferences</i>	38
Segmental aneuploidies of increasing length	39
Phenotypic mapping	43
<i>Critiques</i>	47
<i>Critical regions</i>	50
<i>Small-deletion syndromes</i>	52
Tetrasomy	55

PART III: THE THEORETICAL MECHANISMS AND  
ISSUES: THE PRIMARY AND SECONDARY  
EFFECTS OF ANEUPLOIDY

4. Gene dosage effects	65
Dosage effects in man and mouse	66
Dosage effects in other organisms	78
Dosage compensation	79
<i>Special situations</i>	82
5. Metabolic pathways, transport systems, and receptors	85
Secondary effects of aneuploidy	85
Metabolic pathways and enzyme reactions	86
<i>Theory</i>	86
<i>Experimental and clinical evidence</i>	89
<i>Precedents from the inborn errors of metabolism</i>	93
<i>Increased enzyme activity</i>	98
<i>Inferences</i>	99
Transport systems	100
Receptors	101
<i>Theory</i>	102
<i>Clinical and experimental precedents</i>	108
6. Regulatory systems	113
Theoretical considerations	113
<i>Models of genetic regulation in eukaryotes</i>	115
Regulatory systems in mammals	119
<i>Temporal genes</i>	119
<i>The arylhydrocarbon hydroxylase system</i>	123
<i>Lethal albino deletions</i>	125
Expression of differentiated functions in mammalian cell hybrids	126
<i>Observations</i>	126
<i>Mechanisms</i>	131
<i>Relevance to aneuploidy</i>	134
Regulatory disturbances in aneuploid mammalian cells	135
<i>Search for regulatory disturbances by analysis of cellular proteins</i>	140
Regulatory disturbances in aneuploid nonmammalian cells	143
7. Assembly of macromolecules, cellular interactions, and pattern formation	146

Assembly of macromolecules	146
Cellular interactions	151
Pattern formation	155
8. Type and countertype	159
The search for countercharacters	161
How countercharacters could be generated	167
<i>Digital dermal ridge patterns</i>	170
Do antisyndromes and countercharacters really exist?	172
9. Nonspecific effects of aneuploidy	174
Regulatory disturbance	174
Alterations in the cell cycle and retardation of development	174
<i>The cell cycle and cellular proliferation</i>	174
<i>General retardation of development</i>	177
Disruption of developmental and physiological homeostasis	180
Variability in expression	183
<i>Nongenetic factors</i>	184
<i>Genetic factors</i>	186
Determinants of lethality and severity	190
Polyploidy	195
<i>Tetraploidy</i>	197
<i>Triploidy</i>	200
PART IV: EXPERIMENTAL SYSTEMS FOR THE STUDY OF MAMMALIAN AND HUMAN ANEUPLOIDY	
10. Generation and properties of mouse aneuploids	207
Generation of autosomal aneuploids	207
<i>Full trisomies and monosomies</i>	207
<i>Duplications and deletions (segmental aneuploidy)</i>	210
Properties of autosomal aneuploids	210
<i>Trisomies</i>	212
<i>Monosomies</i>	216
<i>Duplications and deletions (segmental aneuploidy)</i>	220
Chimeras and mosaics	221
<i>Radiation chimeras</i>	221
<i>Aggregation chimeras</i>	224
Teratocarcinoma cells	232
11. Models for human aneuploidy	235

x      *Contents*

Comparative gene mapping	236
<i>Nonhuman primates</i>	236
<i>Autosomal aneuploidy in the mouse</i>	237
<i>X-chromosomal aneuploidy in the mouse</i>	244
Directed aneuploidy	246
<i>Transgenic mice</i>	247
<i>Chromosome-mediated gene transfer</i>	248

## PART V: THREE MAJOR CLINICAL PROBLEMS OF HUMAN ANEUPLOIDY

12. Trisomy 21 (Down syndrome)	253
The structure of human chromosome 21	253
<i>The genetic map</i>	253
<i>The Down syndrome region</i>	255
The effects of unbalancing loci on chromosome 21	259
<i>Superoxide dismutase-1</i>	260
<i>The interferon-<math>\alpha</math> receptor</i>	263
<i>Phosphoribosylglycinamide synthetase and phosphoribosylaminoimidazole synthetase</i>	269
<i>Phosphofructokinase, liver</i>	270
The cellular phenotype of trisomy 21	271
<i>Cell proliferation</i>	272
Sensitivity of cells to radiation and to mutagenic and carcinogenic chemicals	273
<i>Virus-induced chromosome aberrations and cell transformation</i>	277
<i>The <math>\beta</math>-adrenergic response system</i>	279
Platelet serotonin	280
<i>Cellular aggregation</i>	281
Hematological, immunological, and cardiac defects	283
<i>Leukemia</i>	283
<i>Immunological defects</i>	288
<i>Congenital cardiac malformations</i>	297
The nervous system	299
<i>Neuropathology</i>	300
<i>Neurobiology</i>	303
<i>Alzheimer disease</i>	306
An animal model of trisomy 21 (Down syndrome)	311
<i>Comparative mapping</i>	312
<i>The phenotype of mouse trisomy 16</i>	313

	<i>Immunological and hematological development of mouse trisomy 16</i>	318
	<i>Uses of the model</i>	322
13.	Monosomy X (Turner syndrome, gonadal dysgenesis)	324
	Properties of the human X chromosome	324
	<i>The life cycle of the X chromosome</i>	324
	<i>Noninactivation of X-chromosome loci</i>	326
	Mechanisms leading to phenotypic abnormalities	330
	<i>Gonadal dysgenesis</i>	330
	<i>Short stature and congenital malformations</i>	332
	<i>Phenotypic mapping of the X chromosome</i>	336
	<i>The lethality of monosomy X</i>	338
	The 39,X mouse	340
	<i>The XO mouse and 45,X human</i>	343
14.	Cancer	344
	Nonrandom associations of aneuploidy and cancer	345
	Constitutional aneuploidy	346
	<i>Retinoblastoma and the "two-hit" theory of carcinogenesis</i>	347
	Wilms tumor and other forms of constitutional aneuploidy	350
	Acquired aneuploidy	351
	<i>Translocations</i>	351
	<i>Trisomy 15 in mouse lymphoma and leukemia – a prototype</i>	355
	<i>Duplications and trisomies</i>	360
	<i>Deletions and monosomies</i>	361
	<i>Primary versus secondary chromosomal changes</i>	363

## PART VI: CONCLUSION

15.	Principles, mechanisms, and models	369
	Principles	369
	Mechanisms	373
	Models	378
	<i>Appendix: Standard karyotypes of man and mouse and human cytogenetic nomenclature</i>	381
	<i>References</i>	387
	<i>Index</i>	477