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THE CONSEQUENCES OF CHROMOSOME IMBALANCE

Principles, mechanisms, and models

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PRINCIPLES, MECHANISMS, AND MODELS

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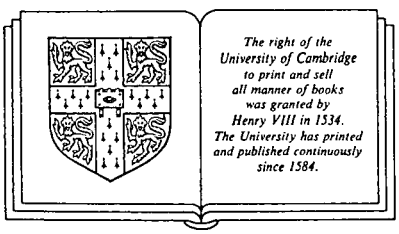

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To Lois, David, Jonathan, Paul, and Joanna
A New Year's resolution finally fulfilled

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

Preface

Gene dosage effects have always held a fascination for me that I cannot readily explain. Perhaps it stems in part from the fact that I entered scientific research at a time when the concepts of genetic regulation – induction, repression, feedback control, adaptive enzymes – were so much in the ascendency, and yet there were clear examples in humans and other mammals of situations in which these concepts did not seem to apply. Two papers had a great influence on my thinking at the time, one by Augustinsson and Olssen (1961), concerned, strangely enough, with enzyme activities in pigs, and the other by Allison and Blumberg (1958), dealing with dominantly and recessively inherited disorders in humans.

Despite my intellectual fascination with gene dosage effects and related matters, I did not, aside from a brief letter to the editor (Epstein, 1964), approach the problem seriously until 1965, when, as a "side project," I looked at the relationship between nuclear DNA content and cell volume in polyploid mammalian liver cells (Epstein, 1967; Epstein and Gatens, 1967). I was immediately struck by the beauty and simplicity of the relationship: over a large range of DNA content, cell volume is quite exactly proportional to ploidy. In 1967, I moved from the National Institutes of Health to the University of California, San Francisco, and in the course of this move switched my principal research focus from the genetic control of three-dimensional protein structure to the genetic control of very early mammalian embryonic development. Once again the opportunity to work on gene dosage effects presented itself, this time in the area of X-chromosome expression during oogenesis and preimplantation embryonic development. Although it had not been planned, the fact that this work, the results of which are presented in detail in Chapter 13, also turned out to be relevant to the understanding of a clinical problem (45,X and gonadal dysgenesis) had special significance for me, for reasons to be discussed next.

While working in the laboratory on early embryonic development, I was also very involved in the clinical aspects of medical genetics. This involvement brought me, and still continues to bring me, into continual contact with individuals with a wide variety of genetic problems and other birth defects. Prominent among these individuals were, of course, those with chromosome abnormalities, especially trisomy 21 (Down syndrome), and I often wondered

about how the presence of an extra chromosome could lead to the devastating outcomes that we encounter clinically. The same type of thinking also applied to monsomy X (45,X) and its effects. While I thought it would be nice to combine these clinical concerns with my more fundamental research interests, and made a tentative move in this direction with studies on the in vitro rates of proliferation of trisomy 21 fibroblasts (Schneider and Epstein, 1972), it took an unexpected set of coincidences to point the way for work on autosomal aneuploidy. My wife, Lois Barth Epstein, had been among the first to recognize the importance of interferon and was working on problems relating to interferon production and action. Imagine then our surprise and delight when one of the first two genes mapped to human chromosome 21 by Tan, Tischfield, and Ruddle (1973) turned out to be the gene responsible for the cellular response to interferon – what we now know to be the gene (*IFRC*) for the interferon-α/β receptor. Given our interests and a ready access to cell strains and individuals with trisomy 21, an entirely new line of research immediately suggested itself. The results of this work are cited in several places, especially Chapter 12, in this volume. Among the many things of importance that have come out of this work – perhaps the most significant, at least in conceptual terms – is the realization that gene dosage effects are just the beginning of the story. To understand the consequences of aneuploidy, it is necessary to begin with gene dosage effects and to then explore their effects on development and function. Ultimately, it is the latter which really matter.

There is yet one more influence to be mentioned, and that is of Alfred Gropp of Lübeck, whose untimely death in 1983 was a severe loss to all scientists interested in aneuploidy. I met Alfred Gropp in 1974 at a conference in Travemunde, at which time I learned for the first time of his ability to breed mice with any type of whole-chromosome trisomy or monosomy at will. Although my first interest in this system was again concerned with the narrow issue of gene dosage effects, it rapidly broadened to encompass the general area of animal (mouse) models for human chromosomal disorders. And, with the continuing interest and collaboration of Alfred Gropp and the encouragement and assistance from the administrators of the National Institute of Child Health and Human Development, it focused once again on the problem of human trisomy 21, this time in the form of the development of an animal model for this condition. All of this will be dealt with in Chapters 10 to 12.

Having spent over twenty years thinking about and working on problems relating to gene dosage effects and, more generally, to the effects of aneuploidy, and having a sabbatical leave available to me, I felt that this would be a good time to take a look at where the field now stands and where it is going. The writing of this book represents my attempt to do so. I have regarded this task as an intellectual journey, one which has taken me into many areas of clinical genetics and basic biology, some of which I have never glimpsed before. Since it would have been pleasurable to have continued the journey,

particularly because of the rapid expansion of relevant literature, it was difficult to know when to stop. However, so that the project could be brought to a conclusion, the survey of the literature was arbitrarily concluded on September 1, 1984, although several additional references were added during the editing of the manuscript.

My overall goals in this volume have been two. The first has been to present a point of view about the effects of aneuploidy – a way of thinking about the problem. In so doing, I have attempted to represent fairly those with whom I might not agree and to identify my own biases for what they are. The second goal has been to bring a sense of coherence to a large mass of clinical and experimental data along with many theoretical considerations. The way in which I have tried to do so reflects, of course, my basic point of view. Nevertheless, the facts still stand for themselves, and their validity is independent of any theoretical construct.

During the writing of this book, there have been many intellectual discoveries. Perhaps the most gratifying of these have been the books and articles that have presented concepts that could be fully appreciated only with hindsight, many years later. Boveri's (1914) theory of the chromosomal basis of malignancy is frequently cited as representing such a view ahead of its time, but two other articles were particularly striking to me – one in which Malcolm Ferguson-Smith (1965) anticipated much of current thinking on X-chromosome aneuploidy and one in which David Comings (1973) did the same for malignancy associated with constitutional aneuploidy. Such discoveries only increase my admiration for the power of the human intellect.

I mentioned earlier some of the individuals who have influenced my thinking along the way, and I would now like to mention a few more: Kurt Benirschke, who introduced me, while I was still a medical student, to the newly emerging field of human cytogenetics; Christian B. Anfinsen, in whose laboratory at the National Institutes of Health I was first exposed to both the intellectual and experimental tools for looking at the relationships between genetics and development; and Arno G. Motulsky, from whom I learned, as a postdoctoral fellow, that even complex problems in clinical genetics can be approached rationally and scientifically.

Throughout my time in research, I have enjoyed the stimulation, collaboration, and assistance of numerous colleagues, fellows, students, and research associates. For much of the work from my own laboratory that is cited throughout this volume, I would like to acknowledge my special debt to my collaborators, David R. Cox, Lois B. Epstein, Terry Magnuson, and Jon Weil, who have devoted much time and effort to the investigation of various problems of aneuploidy and have profoundly influenced my thinking in this area. In addition, I would like to recognize the many research associates who have also acted more in the capacity of collaborators than as technicians in the pursuit of our studies on aneuploidy, in particular Sandra Smith, Joan

Dimpfl, Barbara Hofmeister, Lillian Kwok, Estrella Lamela, Nancy McManus, Bruce Travis, Georgianne Tucker, Della Yee, and Teodosia Zamora. Our work on aneuploidy has been generously supported by the National Institute of Child Health and Human Development, the National Institute of General Medical Sciences, the March of Dimes – Birth Defects Foundation, the American Cancer Society, and the Haas and the Walter Genetic Research Funds.

I wish to thank Jon Weil and David R. Cox for reading and making helpful comments on large sections of the manuscript, Wendy Ovaitt for patiently reducing my execrable scrawl into a finished manuscript on the word processor, Susan Quan for her artistic rendering of the figures, and Norene Parkin for doing so much to facilitate all of our work.

This volume was largely researched and written while I was a Henry J. Kaiser Senior Fellow at the Center for Advanced Study in the Behavioral Sciences, Stanford, California (Gardner Lindzey, director). It is only with the peace and support for sustained intellectual effort that the Center provided that this book could have been completed. And, it is only with the love and encouragement of my wife, Lois, and my children, David, Jonathan, Paul, and Joanna, that the whole project could have been undertaken at all.

Tiburon, June, 1985

Glossary

anal atresia	failure of the anal opening to form
aniridia	absence of the iris of the eye
anophthalmia	absence of the eye
antihelix	the ridge of the external ear that lies anterior to the rim (helix) and behind the concha
arrhinencephaly	absence of the olfactory region of the brain
axial triradial	the point in the palm at which three parallel sets of dermal ridges meet
bicornuate uterus	a uterus which is partially divided into two segments or horns
biparietal diameter	the distance between the parietal bones of the skull (the width of the skull)
blepharoptosis	drooping of the upper eyelid
brachycephaly	a short (in the anteroposterior diameter) head
brachydactyly	short fingers
brachymesophalangia	shortness of the middle phalanges (bones) of the fingers
Brushfield spots	white spots in the iris of the eye (found commonly in Down syndrome)
camptodactyly	flexion contractures of the fingers
caudal hypoplasia	incomplete development of the sacral region
cebocephaly	narrow forehead with flat rudimentary nose and abnormal forebrain
clinodactyly	incurving of the tip of the finger resulting from a wedge-shaped middle phalanx
coloboma	a gap in the iris and/or retina of the eye
concha	the hollow of the external ear into which the ear canal opens
Cornelia de Lange syndrome	a sporadic syndrome characterized by mental retardation, shortness of stature, microcephaly and brachycephaly, bushy

	eyebrows which meet in the midline, small nose and jaw, and increased hair over the body
craniostenosis	deformity of the skull resulting from craniosynostosis
craniosynostosis	premature closure of the cranial sutures (fibrous joints between the flat bones of the skull)
cri-du-chat	cat cry: a syndrome resulting from del(5p) with a characteristic catlike cry in infancy
cryptorchidism	failure of the testes to enter the scrotum
cubitus valgus	lateral angulation of the forearms at the elbows
cyclopia	a single orbital cavity with or without an eye and with either absence of the nose or a tubular nose above the orbit
digital arches	ridges on the finger tips with an archlike pattern
dolichomesophalangia	long, narrow middle phalanges
dolichocephaly	a long, narrow head
ductus arteriosus	a fetal blood vessel between the aorta and the pulmonary artery that normally closes after birth
edema	fluid within tissues
emphysema	overdistension of the lung tissue
endocardial cushion defect	a defect in the tissue that separates the canal between the atria and ventricles of the heart into right and left and contributes to the formation of the tricuspid and mitral valves
enophthalmos	backward displacement (sunkenness) of the eyes
epicanthal fold	fold of skin over the nasal end of the palpebral tissues
equinovarus	a form of club foot in which the foot points downward and inward (medially)
exencephaly	protrusion of the brain through a defect in the skull
exostoses	bony or cartilaginous growths at the ends of the long bones
falciform folds of retina	curved (sickle-shaped) folds in the retina
fontanelles	the skin-covered soft areas in the infant skull at which bone has not yet formed

foramen ovale	an opening between the atria of the heart that is normally closed after birth
fovea	a small pit at the central point of the back of the retina
gonadal dysgenesis	streaklike ovaries devoid of ova found in 45,X (Turner syndrome)
helix	the prominent rim of the external ear
hemangioma	a benign tumor or collection of dilated blood vessels
holoprosencephaly	failure of cleavage of the forebrain during development, with defective formation of the face in the midline
hydatidiform degeneration/ mole	degeneration and proliferation of the epithelium of the chorionic villi of the placenta to form cysts resembling bunches of grapes
hydronephrosis	distension of the collecting system of the kidney resulting from obstruction of the ureter
hydroureter	distension of the ureter resulting from obstruction
hyperphagia	increased food consumption (usually resulting from increased appetite)
hypertelorism	increased distance between the eyes (as measured between the pupils)
hypotelorism	decreased distance between the eyes
hypotonia	decreased muscular tone
Klinefelter syndrome	the syndrome of testicular atrophy and somatic changes resulting from a 47,XXY chromosome constitution
kyphoscoliosis	a backward (hunchback) and lateral curvature of the spine
laryngomalacia	softness of the cartilage of the larynx
limb reduction	absence of bones in the extremities
lobule	the fleshy part of the ear
lordosis	a forward curvature of the spine (hollowback, swayback)
macula	a yellow depression on the back of the retina in the region that is particularly sensitive to color vision
Marfan syndrome	a dominantly inherited connective tissue disorder characterized by long extremities, dislocated lenses in the eyes, and aortic aneurysm

maxillary hypoplasia	underdevelopment of the maxillary (upper jaw) region of the face
Meckel's diverticulum	an occasional appendage or outpouching of the ileum which is derived from the yolk stalk
metopic suture	the fibrous joint between the right and left halves of the frontal bone
microcephaly	small head
micrognathia	small lower jaw
microgyria	abnormally small malformed convolutions of the brain
micropenis	small penis
microphthalmia	small eyes
microstomia	small mouth
Miller-Dieker syndrome	a syndrome characterized by incomplete brain development, often with a smooth surface, microcephaly, severe mental retardation, and facial anomalies
natal teeth	teeth present at birth
neurofibromatosis	a dominantly inherited disorder with multiple soft-tissue tumors of neural origin, often associated with mental retardation
oblique palpebral fissures	lateral upslanting of the eye slits
occiput	back of the skull
orbital	pertaining to the eye sockets
palpebral fissures	the eye slits (space between the eyelids)
pectus excavatum	a depressed sternum (funnel chest)
philtrum	the vertical groove between the nose and the upper lip
polydactyly	extra fingers or toes
postaxial	on the side of the hand or foot opposite the thumb or great toe
Prader-Willi syndrome	a syndrome characterized by mental retardation, obesity with hyperphagia, hypogonadism (small penis, cryptorchidism), small hands and feet, and a characteristic facies
preauricular sinuses/ tags/pits	defects present anterior to the external ear (toward the face)
proptosis	protrusion of the eyes
pterygium	a web of skin on either side of the neck or at a joint
pyloric stenosis	a narrowing of the outflow of the stomach

radio-ulnar synostosis	a bony fusion of the radius and ulna at the elbow
retinoblastoma	a tumor of the eye
retromicrognathia	a small and receding lower jaw
rocker-bottom feet	feet with prominent curvature of the soles resembling the bottom of a rocking chair
Rubenstein-Taybi syndrome	a sporadic syndrome characterized by mental retardation, short stature, small head, broad thumbs, and a beaked nose
scoliosis	lateral curvature of the spine
simian crease	a single transverse crease crossing the palm
strabismus	squint
syndactyly	fusion of the fingers or toes, involving either soft tissue or bone
synostosis	fusion of adjacent bones, as in the skull
thromboembolism	obstruction of a blood vessel by a clot carried from elsewhere in the circulation
thrombocytopenia	a deficiency of blood platelets
trigonocephaly	a triangular-shaped skull with a sharp ridge over the metopic suture, often associated with arrhinencephaly
triphalangeal thumbs	thumbs with three, rather than two bones (phalanges)
truncus arteriosus	a single blood vessel from the heart receiving blood from both ventricles (a combined aorta and pulmonary artery)
turricephaly	a pointed, tower-shaped skull
uvula	the soft part of the palate
Wilms tumor	a malignant embryonal tumor of the kidney that affects young children