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# Developmental genetics

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*Summary.* Of particular concern to the human geneticist are the effects of genetic abnormalities on development. To gain an understanding of these effects it is necessary to engage in a reciprocal process of using knowledge of normal developmental events to elucidate the mechanisms operative in abnormal situations and then of using what is learned about these abnormal situations to expand our understanding of the normal. True developmental genes have not been described in man, although it is likely that they exist, but many developmental abnormalities are ascribable to mutations in genes coding for enzymes and structural proteins. Some of these even produce multiple malformation syndromes with dysmorphic features. These situations provide a precedent for asserting that not only monogenic developmental abnormalities, but also abnormalities resulting from chromosome imbalance must ultimately be explicable in molecular terms. However, the major problem confronted by the investigator interested in the pathogenesis of any of the chromosome anomaly syndromes is to understand how the presence of an extra set of normal genes or the loss of one of two sets of genes has an adverse effect on development. Several molecular mechanisms for which limited precedents exist may be considered on theoretical grounds. Because of the difficulties in studying developmental disorders in man, a variety of experimental systems have been employed. Particularly useful has been the mouse, which provides models for both monogenic and aneuploidy produced abnormalities of development. An example of the former is the mutation oligosyndactylism which in the heterozygous state causes oligosyndactyly and in the homozygous state causes early embryonic mitotic arrest. All whole arm trisomies and monosomies of the mouse can be produced experimentally, and of special interest is mouse trisomy 16 which has been developed as an animal

model of human trisomy 21 (Down syndrome). In the long run, the most direct approach to elucidating the genetic problems of human development will involve not only the study of man himself but also of the appropriate experimental models in other species.
*Key words.* Developmental genes; developmental disorders; chromosome abnormalities; animal models.

*Introduction*

The term 'developmental genetics' is generally used to cover all aspects of the genetic control of development and as such encompasses a variety of areas ranging from the structure of the genome and the regulation of gene expression to the genetic control of differentiation and morphogenesis and the effects of genetic abnormalities on developmental processes. Clearly, none of these problems is unique to any organism or species, and a large variety of diverse organisms are being used to study them. Particularly in vogue as eukaryotic experimental systems have been yeast, sea urchins, worms (leeches, *Chaenorabditis elegans), Drosophila, Xenopus,* and the mouse. Each has been chosen because of a combination of genetic, molecular, and/or developmental characteristics that make it especially attractive for investigation, and information obtained from one organism is, with appropriate concern for species differences, applicable not only to the others but to man as well. However, the human geneticist, while certainly interested in all of the areas of developmental genetics mentioned above, has special reasons for being concerned with the last – the effects of genetic abnormalities on developmental processes. A significant morbidity and mortality is associated with genetically caused abnormalities of development at all stages of human life, from conception to the adult years. The term 'abnormality of development' can certainly be interpreted in a variety of ways, but for the purposes of this discussion I shall use it to refer to abnormalities of tissue differentiation, organogenesis, and morphogenesis which may lead to death, congenital or postnatally acquired malformations, and/or impairment of function.

In an earlier review of the subject of developmental genetics, I drew an analogy, which I think is worth reiterating, between human biochemical genetics and human developmental genetics as I hoped it would evolve[33]. I pointed out that one of the great accomplishments of the past century, certainly since the time of Garrod, has been the exploitation of human biochemical genetics for the elucidation of many of the intricate details of intermediary metabolism. Starting with a general knowledge of biochemical processes, the analysis of a large number of biochemical defects has led and continues to lead to the discovery and investigation of many unsuspected pathways. Once this had occurred, knowledge of these pathways permitted the explanation of still other genetically caused metabolic abnormalities. I referred to this process as a reciprocal one, in which knowledge of normal biochemical mechanisms permits an elucidation of genetically caused abnormalities of metabolism and the information gained from investigation of the latter enhances our understanding of the normal. It is exactly this same reciprocal process which I would like to see occur in the area of human developmental genetics. Knowledge of normal developmental phenomena and their genetic control should permit an understanding of how a genetic abnormality or even an environmental insult results in aberrant development. Reciprocally, analysis of situations in which development is aberrant should increase our understanding of the mechanisms of normal development. What is now required is to attack these problems of human development from the mechanistic as well as the descriptive point of view.

*Developmental genes*

A particular concern of investigators in the broader field of developmental genetics has been the search for genes which may be regarded as developmental genes in that they control major developmental processes. The prototypes of such genes are those defined by the homeotic mutations in *Drosophila*, mutations which affect such general processes as pattern formation (segmentation and the identification of anterior and posterior) and the determination of the identity of specific structures[77, 85, 103]. These genes are contrasted with other genes which, while potentially leading to abnormalities of development when mutant, are concerned with more common metabolic or structural functions. Presumably, developmental genes responsible for the regulation of major developmental processes exist in man and other mammals, but none have as yet been identified. The closest we have come are the *trans*-acting temporal genes which control the activites of specific enzymes (for which they are not the structural genes) in specific organs, but they certainly do not have the same broad regulatory power which we associate with the *Drosophila* developmental genes[93]. However, the recent discovery that sequences homologous to the *Drosophila* 'homeobox' genes are also present in the genomes of man and mouse raise the possibility that such developmental genes may actually exist in mammals[70, 71, 97].

Evidence for the existence of genes directly involved in the regulation of the expression of tissue specific functions in human and other mammalian cells has been obtained from the analysis of somatic cell heterokaryons and hybrids formed between cells which are dissimilar in type. Depending on the nature of the cells combined, tissue specific functions may either be extinguished or retained and, in some instances, a nucleus of one type may be reprogrammed to code for the synthesis of gene products characteristic of the other[9, 120]. Analysis of these hybrids and heterokaryons suggests the existence of both positive and negative soluble regulatory factors which must, in turn, be coded for by genes which may be considered as regulatory in nature. The nature of both the regulatory substances and the genes which determine them remains to be elucidated.

However, from the point of view of understanding the genetic basis of *abnormalities* of development in man, it is not necessary that we restrict our interest only to such putative developmental genes – identification of abnor-

malities of enzymes, structural proteins, surface antigens, and the like may be just as meaningful in many situations. While not necessarily the controlling factors in normal development, these products and the genes which control them are the substrate upon which normal development must take place. Furthermore, it may turn out that in the environment of a particular type of cell or tissue, a gene product which in other tissues has no particular developmental function may be specifically involved in the developmental process under study. We should, therefore, keep an open mind about what kinds of abnormalities to search for and their significance when identified when we investigate the pathogenesis of genetic abnormalities affecting human development. For example, the gene for the enzyme, adenosine deaminase, does not regulate lymphocyte production. However, its abnormality, which results in loss of enzyme activity, does have effects that are highly deleterious, in a quite specific manner, to lymphocytes and results in severe combined immunodeficiency disease[86]. Interestingly, there may also be an associated chondro-osseous dysplasia with multiple skeletal abnormalities[19, 86].

*Genetically determined developmental disorders*

Of the totality of genetically determined disorders that have been identified, those which may be considered as developmental abnormalities make up a significant component. Close to 0.75% of newborns in the United States have a congenital malformation which may have, in part, a genetic etiology, and figures twice as great have been obtained in England[30, 68]. The malformations include spina bifida and anencephaly, congenital heart defects, cleft lip and cleft palate, talipes equinovarus, and dislocated hips, the first three of which (amounting to 0.5% of US newborns) certainly represent abnormalities of organogenesis and morphogenesis. In addition, it is estimated that about 0.2% of newborns have autosomal chromosomal abnormalities, all associated with congenital malformations, and another 0.03% have sex chromosome abnormalities (not including XXX, XXY, or XYY) which are developmentally deleterious[69]. Finally, there is a large number of Mendelian (monogenic) disorders producing developmental defects which in the aggregate may affect 0.05–0.1% of newborns[30, 100]. Thus, a relatively conservative estimate is that about 1% of human newborns have a genetically caused or influenced developmental disorder affecting structure and possibly function as well. Looking at it another way, congenital abnormalities, associated principally with chromosome abnormalities, are responsible for loss of 10–20% of conceptions during pregnancy[11]. Further, congenital anomalies of all types are the third leading cause of death (after accidents and cancer) of children ages 1–14 years[2].

Although much has been written about developmental thresholds and the etiology of congenital defects[52], the precise roles that genetic factors play in the common congenital malformations of the neural tube-congenital heart-facial clefting group are not at all understood. The likelihood of identifying specific responsible loci seems, in the short-run, to be very small indeed. However, one possibility which does exist is that, at least in some instances, the genetic factor(s) is one which directly determines susceptibility to some external agent, such as a teratogen, which is actually required to produce the defect. Instances of this type, in which single genetic loci can be implicated, exist in the animal and human teratology literature[15, 87, 105]. For example, of two human female fraternal twins exposed to diphenylhydantoin in utero, the one with a low fibroblast activity of the detoxifying enzyme, epoxide hydralase, was the one who also developed the fetal hydantoin syndrome[15, 109].

*Inherited disorders of development*

All modes of Mendelian inheritance may be involved in the etiology of inherited disorders of development. In a recent analysis it was found that about one quarter of known monogenic disorders could be considered as involving malformations or errors of morphogenesis[21]. Of these, 53% were autosomal dominantly inherited, 40% autosomal recessively, and 8% X-linked. This contrasted with proportions of 38%, 52%, and 10%, respectively, for conditions considered to be metabolic or functional. The malformations most often involved the musculoskeletal system (35%), limbs (31%), and craniofacial structures (29%), and over half the time more than one system was affected. In presenting these data, the authors commented on the differences in proportions of autosomal dominant and recessive modes of inheritance in the two groups and suggested that the large proportion of autosomal dominant phenotypes among the malformations is probably a reflection of the involvement of a large number of non-catalytic gene products with short periods of function in morphogenesis[21]. In this assessment, they were appealing to the generally held, although not universally true, belief that dominantly inherited conditions involve deficiencies or abnormalities of structural and related proteins while recessively inherited conditions are the result of enzyme defects[32]. However, even allowing for the fact that quantitative differences in the modes of inheritance do exist, the more impressive fact, to me at least, is that all modes of inheritance are represented to a significant degree. This would imply, if the same reasoning were to be followed, that *all* types of genes and gene products must be considered in the etiology of disorders of development.

*Recessively inherited disorders*

Evidence for this conclusion is now being accumulated from studies of a variety of conditions which affect development in one way or another. While many of these disorders might be put into the category of biochemical defects, since known biochemical aberrations are involved, they belong in the present discussion because physical development is also affected. In fact, it is the existence of this group of conditions that points out how thin the line between development and biochemical genetics actually is – if it actually exists at all. Consider, for example, the several recessively inherited human disorders of mucopolysaccharide degradation, resulting from specific enzyme deficiencies, which give rise in different degrees to abnormalities of skeletal growth, mental retardation, corneal opacification, and deafness[79]. For some of these features the fault may lie with the deposition of

undegraded mucopolysaccharide in a particularly vulnerable tissue, thereby directly interferring with function. But in others, such as the development of the skeleton, the problem must be more subtle. Something about the inability to degrade mucopolysaccharides, and therefore to control properly the glycosaminoglycan composition of developing cartilage and bone, leads to gross abnormalities of skeletal growth and modeling. Were we unaware of the metabolic defects, many of the mucopolysaccharidosis would be categorized as multiple abnormality syndromes affecting the skeleton, central nervous system, and other organs. In this regard it is of interest that another multiple congenital anomaly syndrome with just these attributes, the Coffin-Lowry syndrome, has been found to have abnormalities of proteoglycans in cultured skin fibroblasts[6].

Two other recessively inherited metabolic defects have been implicated in the genesis of congenital malformations. One is glutaric aciduria type II, thought to result from a defect leading to multiple acyl-CoA dehydrogenase deficiency. Numerous malformations have been reported in affected newborns including craniotabes, abnormal facial folds with upturned nose, bell-shaped thorax, rocker bottom feet, urinary tract abnormalities, multiple renal cysts, and pachygyrria or polymicrogyria of the cortex[10, 55, 73]. These abnormalities have been attributed to the teratogenic effects of severe metabolic derangements within the fetus, with poisoning of the mitochondria, impairment of energy production, and cellular death. The brain and kidneys are considered to be particularly vulnerable.

The other recessively inherited metabolic abnormality associated with malformations, perhaps not wholly unrelated to glutaric aciduria type II, is the Zellweger or cerebrohepatorenal syndrome[75]. This condition is characterized by craniofacial anomalies which typically include a high forehead, upslanting palpebral fissures, hypoplastic supraorbital ridges, Brushfield spots, epicanthic folds, and very large fontanels. Macrocephaly, high arched or posterior cleft palate, hypertelorism, and abnormal ear helices may also be present. The other consistent features are profound hypotonia, pigmentary retinopathy, hepatomegaly with neonatal or later onset jaundice, talipes equinovarus (club feet), renal cysts, and profound retardation. Development of the brain is abnormal. Peroxisomes are absent in liver and kidney, and the mitochondria are severely dysfunctional. Numerous metabolic abnormalities affecting glucose and glycogen, iron, bilirubin, bile acids, pipecolic acid, and organic acid metabolism have been identified[75]. The biosynthesis of phosphatidylethanolamine and phosphatidylcholine plasmalogens, major phospholipid components of cellular membranes, is profoundly deficient in brain, heart, and kidney[66]. The basic genetic defect in this condition is unknown. Although mitochondrial oxidative function is defective in all organs examined, it has been suggested that the biosynthesis of the peroxisomes themselves may be the fundamental problem[66, 101].

The last two examples make it clear that metabolic defects, either the direct result of enzyme deficiency or of defects which secondarily lead to enzyme deficiencies, may produce abnormalities of structure and features which are characterized as being dysmorphic. In both these are also more generalized metabolic abnormalities which are probably the result of interference with the integrity of major cellular organelles (mitochondria, peroxisomes). Nevertheless, the essential point is that apparently characteristic abnormalities of development, with specific dysmorphic features, can result from what are generally considered to be inborn errors of metabolism. How the developmental abnormalities actually occur is, of course, still unknown. However, in this regard, as well as with regard to the relationship between developmental defects and metabolic disorders, the following comment of Opitz on the Zellweger syndrome is of interest: 'Initially we viewed it as a true multiple congenital anomalies (MCA), i.e., malformation syndrome. In this case it is marvelous to see how hindsight can improve the clinician's understanding of the pathogenetic nature of a given syndrome. For in view of the severe generalized mitochondrial oxidative defect, the developmental manifestations of the Zellweger syndrome can only be regarded as results of a prenatal *metabolic dysplasia* which mostly results in anomalies of *incomplete development*'[53]. I think that Opitz' emphasis is misplaced. The real point is that the Zellweger syndrome *is* a multiple congenital anomaly syndrome (a pattern of multiple anomalies thought to be pathogenetically related[107]) for which a metabolic etiology has been defined. The existence of an etiology does not alter the reality of the syndrome.

### *Dominantly inherited disorders*

Developmental defects can also be associated with abnormalities of structural proteins. Recent advances in our understanding of the chemistry of collagen has permitted the elucidation of several inherited disorders, predominantly autosomal dominant in transmission, which affect growth of the skeleton as well as the integrity of other tissues. While I would not go so far as to assert that individuals with these connective tissue disorders are dysmorphic in the same sense as those with the syndromes just discussed, their development is nevertheless certainly abnormal. Spranger et al. refer to these conditions as dysplasias, the morphological results of the abnormal organization of tissues, rather than malformations which result form intrinsically abnormal developmental processes[107]. It is the same distinction that underlay the comment of Opitz just alluded to.

The connective tissue disorders can be divided into three principal groups: the osteogenesis imperfectas, in which the major abnormalities are in the bone; Marfan syndrome, in which these are abnormalities in many systems; and the Ehlers Danlos syndromes, in which the skin and connective tissue are particularly vulnerable[67]. For this discussion I shall consider only the first two. The important result of the work on osteogenesis imperfecta is that defects in collagen synthesis, resulting from either absence or abnormality of specific collagen chains, can lead to abnormal modeling and strength of bone. A variety of structural collagen defects have been defined, including deletions, elongations, and amino acid substitutions. These structural abnormalities in individual collagen chains result, in turn, in abnormalities of post-translational modification, stability, and assembly, the net effect of which is to produce less or weaker collagen[16, 96, 111, 121]. In

some cases, synthesis of a specific collagen chain is reduced by 50% as the result of mutation, again with a reduction in the formation of mature collagen molecules[4,99].

The Marfan syndrome is a group of disorders in which the major abnormalities involve numerous systems, including the skeleton, joints, eyes, and heart. Directly or indirectly, all of the abnormalities, which include elongation of the long bones, abnormalities of the sternum and spine, dislocation of the lenses, vaulting of the palate, and aortic and cardiac valve dilation, are attributable to a defect or defects of connective tissue. Although progress has been relatively slow in defining these defects precisely, there have been reports of a deficiency of chemically stable collagen cross-links in skin and aorta[12], and, in one patient only, of an abnormal type I collagen $\alpha 2$ chain with a short amino acid insertion[17]. The latter abnormality also resulted in defective crosslinking.

I think there are two major lessons to be derived from the work on the connective tissue disorders. The first is that a large number of clinically and genetically distinguishable disorders can arise from defects of individual collagen chains, indicating a high degree of specificity in the functions of each of the chains and in the perturbations which result from their abnormality. The second is that defects in the structure of macromolecules can have widespread but nonetheless specific effects on development. By extension, it should therefore be possible to explain disparate and widespread developmental effects of many mutations on a strict biochemical basis rather than having always to appeal to the concept of a polytopic developmental field in which the affected components were, at one time in development, spacially close to one another or were otherwise related by long range inductive effects[90,107].

While none of the examples discussed so far is perfect, I have devoted considerable attention to them to make the point that we should not regard genetically determined abnormalities as being anything mysterious. Ultimately, they must be explicable, at least at the basic level, in molecular terms. A change in the structure or expression of a gene or group of genes must, if it is to have any effect, be reflected in a change in the structure, concentration, and/or time of appearance of the gene products which they control. These biochemical changes, in turn, may affect any or several of the vast number of processes involved in differentiation and morphogenesis. Sometimes the pathways from the basic defect(s) to the observed abnormalities may be very tortuous and difficult to trace. However, they must exist and once traced will provide, as I suggested at the outset, considerable information not only about the process of abnormal development but about normal development as well.

### *Chromosome abnormalities*

The same reasoning also applies to chromosome abnormalities and to their role in the causation of congenital anomalies. Despite suggestions to the contrary[104], I believe that it should ultimately become possible to dissect the phenotypes associated with individual aneuploid states into constituent parts explicable on the basis of one or a combination of specific biochemical aberrations[40]. I am led to this belief from two directions. First, even though there is considerable overlap among the features of different aneuploid states and variability in the features of individual states, there are nonetheless generally consistent patterns of anomalies which make it possible to identify and discriminate among the different conditions. In other words, the signals are more important than the noise in pointing to the specificity of phenotypes and therefore lead to the inference that the relationship between a state of chromosome unbalance and the resulting phenotype is, if not a necessarily direct one, nonetheless a specific one.

Second, each state of aneuploidy is associated with the quantitative imbalance of a particular set of genes, each with its own specific function. All of the evidence now available (for over 40 loci in man and mouse) indicates that these changes in gene dosage result in quite commensurate gene dosage effects for the gene products that are determined by the affected loci[40]. Furthermore, examination of two-dimensional polyacrylamide electrophoretic gel patterns of polypeptides of cell and tissue extracts from individuals with various forms of autosomal aneuploidy, including human trisomy 21, several mouse trisomies and one mouse monosomy, and even trisomy for chromosome arm 2L of *Drosophila,* does *not* reveal the presence of widespread alterations in gene expression[45,76,84,114,117]. Therefore, the immediate effects of chromosome imbalance appear to be principally on the gene products for which the unbalanced region codes and on the functions which these products have. These must, therefore, be responsible for the phenotypic abnormalities which result, with causal pathways which, as in the case of the monogenic developmental disorders, may range from quite direct to extremely tortuous – but always specific.

The major problem confronted by the investigator interested in the pathogenesis of any of the chromosome abnormality syndromes is to understand how the presence of an extra set of *normal* genes (in a duplication or trisomy) or the loss of one of two sets of genes (in a deletion or monosomy) has an adverse effect or development. In neither situation are we dealing with abnormal gene products, so the mechanisms that might apply, for example, in the connective tissue disorders in which one of the collagen chains is structurally abnormal are not relevant. On theoretical grounds several types of molecular abnormalities may be considered, but in each instance it is essential to translate a quantitative gene dosage effect (plus or minus 50%) into an abnormality of function[45]. These molecular abnormalities include the effects of changing the concentrations of rate-limiting enzymes, receptors, regulatory molecules, structural macromolecules, cell surface constituents required for recognition and/or adhesion, and molecules involved in pattern formation[40]. A limited number of precedents which relate quantitative changes in gene-product synthesis and concentration to deleterious or, at least, altered developmental and functional outcomes already exist in several of these categories. Among these are the porphyrias which result from a 50% deficiency of one of several enzymes in the porphyrin biosynthetic pathway, familial hypercholesterolemia caused by a deficiency of low density lipoprotein receptors, $\alpha$ thalassemia minor with dele-

tion of two of the four α globin genes, thromboembolism in individuals with reduced levels of plasminogen or antithrombin III, and hereditary elliptocytosis due to a 50% decrease in red cell skeletal membrane protein band 4.1[3, 54, 63, 102, 116]. Osteogenesis imperfecta resulting from a deficiency in collagen synthesis has already been mentioned. While each of these abnormalities is the result of a deficiency of gene product, such as might occur in a monosomy or deletion, it is likely that similar precedents will appear for increases in the level of gene product. The only one that presently comes to mind is hyperuricemia resulting from increased activity of the enzyme phosphoribosylpyrophosphate synthetase[7]. All of these precedents refer, of course, to known metabolic or structural protein disorders, but they do reinforce the assertion that changes in gene-product concentrations of the order of 50% can have significant metabolic or structural effects. Therefore, as I have already suggested, the real challenge in understanding how aneuploidy produces its untoward effects is to determine which unbalanced loci are actually affecting development and function and how these effects interact to produce a particular aneuploid phenotype. These issues are treated in much greater detail in a monograph on the effects of aneuploidy which has just been published[40].

*Trisomy 21*

Among the human chromosome disorders, greatest interest with regard to the mechanisms involved has not unexpectedly centered on trisomy 21 (Down syndrome). It is the most common chromosomal abnormality found in newborns, as well as the most frequent specific cause of human mental retardation and congenital heart disease. Other features include a wide variety of congenital anomalies which produce the typical physical phenotype of Down syndrome, immune defects, an increased susceptibility of leukemia, and, in adult years, the development of the neuropathological changes of Alzheimer disease (presenile dementia)[36, 106]. As with the other human chromosome disorders, little is known about the mechanisms by which trisomy 21 interferes with normal development and function to produce these features of the Down syndrome phenotype. However, with the recent progress in the mapping of the human genome, it has been possible to look at the functions of genes known to be on chromosome 21 and to examine what effects their imbalance might have.

Among the genes mapped to human chromosome 21 are those for cytoplasmic superoxide dismutase *(SOD-1)*, for the receptor for α- and β- interferon *(IFRC* or *IFNRA)*, and for phosphoribosylglycinamide synthetase *(PRGS)*. Uncompensated dosage effects have been shown for the products of each of these genes, with a 50% increase in concentration over normal being found in trisomy 21 cells, usually fibroblasts[5, 47, 51]. Furthermore, in the case of the interferon receptor, it has been shown that the induction of several intracellular polypeptides and of the enzyme (2′–5′) oligoisoadenylate synthetase is also 50% greater in trisomy 21 than in matched diploid fibroblasts, so that these immediate biochemical responses directly reflect gene dosage[118, 119]. However, when compared for several biological effects, especially antiviral and antiproliferative responses, trisomy 21 cells turn out to be from three- to ten-fold more sensitive than are the diploid controls[41, 118]. Thus, the primary gene dosage effect is amplified at one or more steps in the interferon response system by mechanisms which remain to be elucidated. The existence of this amplification in the interferon response system provides a valuable example of and useful experimental model for how a relatively small gene dosage effect can, under appropriate circumstances, result in much more pronounced functional consequences.

In view of its magnitude, it would be tempting to ascribe some feature or features of Down syndrome to imbalance of the α-interferon receptor locus. However, at the present time it is not possible to draw such an inference. Furthermore, as I have already suggested, it is highly unlikely (although not inconceivable) that the phenotype produced by trisomy 21 is produced by imbalances of just one or a few loci. More likely is the assumption that the phenotype which we observe is the cumulative effect of the increased concentrations of several or even a large number of gene products, not just one or two. Nevertheless, it is certainly possible that certain loci, such as *IFRC*, may play a prominant role in the development of a specific phenotypic feature or set of features. Unfortunately, this is difficult to test in aneuploid humans.

*Animal models for human developmental disorders*

The study of human developmental disorders is limited to a great extent by our inability to investigate developmental processes in humans. For this reason, the use of animal models has become quite attractive, and the mouse has become the experimental animal of choice. The reasons for this are several and include the following[34, 44]: 1) a large number of genetically caused (monogenic) developmental disorders, many similar to conditions in humans, are known, and breeding stocks are available in the mouse; 2) monosomy and trisomy can be generated for all of the mouse chromosomes and, in come instances, deletions and duplications can also be generated; 3) the developmental analysis of the pathogenesis of abnormalities, particularly during crucial stages of organogenesis, can be readily carried out; 4) unlike humans, in which relatively few tissues can be studied, all cells and tissues of the mouse are available for investigation; 5) in the case of conditions affecting early embryogenesis, pre- and early postimplantation stages of development can be analyzed; 6) the effects of genetic and environmental factors on the expression of the mutant or aneuploid phenotype can be assessed; and 7) proposed therapeutic approaches can be studied.

In the case of the monogenic disorders, developmental defects affecting virtually every individual system and various combinations of systems have been identified, and all modes of inheritance are represented[56]. In many cases the responsible genes have been mapped to specific chromosomes or chromosomal regions, and attempts are being made in several to ascertain the specific nature of the mutations and of the affected gene products. Particularly promising in this regard has been the study of the inherited developmental abnormalities of the nervous system and of the limbs as well as the *t*-complex muta-

tions which lead to a wide variety of developmental abnormalities at different stages of embryogenesis[18, 29, 74, 78, 122]. In addition, analysis of genetically more complex situations, such as the susceptibility to the teratogenic induction of facial clefting, are also producing quite interesting results[8].

*Oligosyndactylism*

Particularly intriguing in the mouse are a series of mutations which in the heterozygous state cause developmental abnormalities and in the homozygous state result in early embryonic lethality[80, 81]. On the assumption that it might be easier to uncover the molecular abnormality in the homozygote, in which it is fully expressed and has more severe consequences, rather than in the heterozygote in which the normal gene product is also being made, Dr Terry Magnuson and I studied the homozygous form of one of these mutations, oligosydactylism *(Os)*. This mutation should, because of its heterozygous phenotype, be of particular interest to the human geneticist. In the heterozygous state *(Os/+)*, this mutation leads to a dominantly inherited abnormality of the limbs, with fusion of the second and third and sometimes the fourth digit in all feet[62]. Fusion of the digits may be so complete as to result in a four-toed foot and has been attributed to a reduction in the size of the preaxial margin of the foot plate which is detectable midway through gestation. This condition therefore becomes a model for a large number of human inherited conditions in which syndactyly or fusion of the digits is a prominent feature[113]. In addition to the skeletal defects, muscular anomalies with abnormal fusions or insertions of muscles or tendons have also been observed, as has a nephrogenic diabetes insipidus which results from a severe reduction in the number of glomeruli and functional nephrons[72, 108]. In the homozygous state *(Os/Os)*, the phenotype is very different and very striking. Embryonic development is arrested after the sixth cleavage, with the appearance of metaphase figures which resemble those seen after prolonged treatment of cells with a mitotic inhibitor such as vinblastine or colcemid[94, 115]. The existence of such a mitotic defect, which is so far unique in mammals, suggests an abnormality in the formation or disaggregation of the spindle, either because of some intrinsic abnormality in one of the components of the spindle (such as tubulin or the microtubule-associated proteins) or in a metabolic system required for spindle formation or disaggregation or for chromosome movement. It is clear from our studies to date that mitotic spindles are actually formed and accumulate in large numbers in the arrest embryonic cells[82]. These spindles can be disaggregated and reaggregated with appropriate treatments, and these mechanical aspects of spindle formation do not appear to be abnormal. Similarly, we have been unsuccessful so far in demonstrating any abnormality in tubulin, the major structural component of the mitotic spindle, and the abnormality appears therefore to reside in the mechanism of chromosome separation following formation of the metaphase plate.

We are, of course, interested in the oligosyndactylism mutation because of its striking effects on early development and, especially, on the process of mitosis. However, in the context of the present review, I would like to emphasize another reason for our interest. The heterozygous manifestations, particularly the limb defects, represent a class of relatively common dominantly inherited human morphogenetic abnormalities for which we presently have no mechanistic interpretation – or even a conceptual basis on which to propose such an interpretation. However, the elucidation of the molecular basis of the developmental abnormalities associated with the homozygous state, for which valuable clues already exist, will provide the conceptual basis necessary for the analysis of the skeletal and other heterozygous manifestations of this condition and hopefully of other conditions, human and mouse, of a similar type.

*Models for chromosome disorders*

The use of the mouse to study the pathogenesis of disorders resulting from autosomal chromosome imbalance was pioneered by Gropp and his collaborators[61]. They capitalized on the facts that aneuploid progeny can be bred in high frequencies (about 15–20% each for monosomies and trisomies) from balanced parents which carry one or two metacentric (Robertsonian fusion) chromosomes and that the necessary metacentric chromosomes exist in groups of feral mice living in relatively circumscribed geographical areas[59]. The first identified of these feral strains was *M. musculus poschiavinus* which has seven pairs of fusion chromosomes, thereby reducing the total chromosome number from 40 to 26. At the present time approximately 60 different metacentric chromosome combinations are known[39, 44, 59]. Fortunately the feral mice carrying the fusion chromosomes are interfertile with laboratory strains, and it has been possible to transfer these chromosomes individually into the latter.

The breeding scheme now in general use makes use of, in most instances, a male parent carrying two different metacentric chromosomes which share one arm in common. This arrangement leads to a high rate of nondisjunction for the shared chromosome arm and production of progeny aneuploid only for that arm. By this means, each of the 19 whole-arm autosomal trisomics of the mouse has been produced and examined, as have several of the whole arm monosomics[39, 44, 58]. All of the monosomics die early in gestation, with several probably dying prior to implantation and none surviving significantly beyond it[28, 42, 83, 84]. Similarly, although they do survive until at least midgestation, all of the mouse trisomics, with the exceptions of trisomy 19 and to a lesser extent trisomies 16 and 18, die prior to parturition[39]. The precise cause of death of the trisomics is not known. In some instances it appears to be related to extremely poor embryonic growth and development. In others, it has been suggested that death may be caused by relative placental insufficiency, with the aneuploid placenta being unable to serve the metabolic needs of the aneuploid fetus[57].

With respect to their early times of death, the mouse trisomics are not significantly different from the human trisomics. Even in the case of trisomy 21, the most viable of the human trisomics, approximately 75% of the recognizable trisomic embryos and fetuses die during gestation[14]. Similarly, the very early demise of the mouse monosomics is consistent with what is known about the

human situation, since virtually no whole-arm or even partial autosomal monosomics are found in large series of karyotyped human newborns or abortuses[13, 64, 88].

The phenotypes of the mouse aneuploids are as specific as they are in humans and are no less diverse. The phenotypes described for the individual mouse whole-chromosome trisomies include a variety of interesting developmental lesions including holoprosencephaly, congenital heart disease, and exencephaly (see references 39 and 44 for summary). As might be expected, given the differences in chromosome structure between mouse and man, none of the mouse trisomics precisely mimics any of the human trisomics. Nevertheless, interesting phenotypic parallels can be drawn and, as will be illustrated shortly, genetic parallels as well.

Although the aneuploid embryos and fetuses generated as just described can be used for a large variety of studies of the effects of chromosome imbalance on development, it is desirable to have viable aneuploid mice for the investigation of functions, such as neurological function, immune responses, and reactions to environmental agents, that are primarily of interest in postnatal animals. One approach to this goal is to rescue the aneuploid cells by incorporating them into mosaic or chimeric animals composed of both aneuploid and normal cells, and two ways of achieving this have been explored. One makes use of the construction of radiation chimeras in which irradiated animals are repopulated with stem cells from livers of aneuploid fetuses[65]. Our own approach to the problem has been to construct aggregation chimeras by aggregating aneuploid and diploid preimplantation embryos and then transferring the aggregates back into pseudopregnant females. This method has now been successfully used for three of the mouse trisomies, trisomies 15, 16 and 17, and in each case liveborn chimeras composed of both types of cells have been produced[27, 48, 49]. The chimerism extends to virtually all organs and tissues of the animal, although in certain instances specific tissues seem to be composed predominantly or entirely of non-aneuploid cells. Particularly striking in this regard are the lymphoid and hematopoietic systems of trisomy 15↔2n and trisomy 16↔2n chimeras, in which virtually no trisomic cells are detectable[27, 44]. With only one exception, liveborn monosomy↔diploid chimeras have not been observed, suggesting that monosomic cells are either intrinsically inviable or are unable to compete with normal ones as proliferation and development proceed[48, 84].

In suggesting the use of the mouse as a model for human chromosome disorders, it is necessary to be very explicit about what it is a model of and how it might be used. Clearly, one should not expect that it will be possible to replicate in the mouse the complete phenotypes of specific human disorders, especially those resulting from trisomy or monosomy of whole chromosomes or major portions of chromosomes. Although there is evidence for the conservation of synteny of small groups of genes[20], indicating that segments of the genome may be maintained intact throughout mammalian evolution, cytogenetic and gene mapping evidence suggests that it is highly unlikely that this is the case for whole chromosomes or large chromosome segments. Nevertheless, a model system would, under favorable circumstances, permit the construction of a mouse in which several genes present on a human chromosome of interest are simultaneously unbalanced in a single animal.

Two principal uses of such a model can be suggested. The first is to look at the developmental, metabolic, and physiologic consequences of unbalancing specific loci. This model thus provides a means for determining whether imbalance of one or more of these loci is etiologically involved in the observed phenotypic abnormalities. The second use is to investigate phenomena which occur in both the human and the corresponding mouse aneuploids, even though the specific loci involved are, for the moment, unknown. In contrast to the first approach, which is essentially deductive in nature in that it starts with known loci and proceeds to an exploration of the effects of this imbalance, the second approach works in reverse and may be considered inductive. It starts with observed phenomena and attempts to discover the mechanisms of their pathogenesis and, ultimately, how these mechanisms are related to genes present on the unbalanced chromosomes. The assumption is made that if the phenomena are specific and reasonably similar in the human and the mouse, then the underlying mechanisms are likely to be the same or similar.

### *A model for trisomy 21 (Down syndrome)*

Our work with mouse models for aneuploidy has focused principally on monosomy-X (XO)[35, 37, 38], autosomal monosomy[83, 84] and on developing an animal model for human trisomy 21. Only the last of these will be considered here. To create a model for human trisomy 21 it was necessary to map the genes known to be present on human chromosome 21 onto the mouse genome and to determine whether there is a chromosome segment or segments in the mouse homologous to regions of chromosome 21. Therefore, three of the genes known to be on chromosome 21 *SOD-1, IFRC,* and *PRGS,* were mapped by somatic cell genetic techniques, and all were found to be on mouse chromosome 16[23–25]. Further, the two, *SOD-1* and *PRGS,* which are known to be on band 21q22 in man[26], the region which in the trisomic state is associated with the Down syndrome phenotype[110], have been mapped to the distal segment of mouse 16[23]. The existence of the conserved synteny of the three genes that have been mapped provides a basis for hoping that all three genes, as well as many others still undefined, are present in homologous human and mouse chromosome segments.

The salient features of mouse trisomy 16 include mild growth retardation, a severe but often transient edema, open eye lids, brain hypoplasia, and inner ear abnormalities[39, 42, 60, 91, 92]. Congenital heart disease affecting the great vessels is almost invariant, and an endocardial cushion defect (common atrioventricular canal) is observed in about half of the fetuses[89]. The last of these is of great interest since the same lesion is found in about half of newborns with Down syndrome[98]. However, considering the prenatal or perinatal lethality of mouse trisomy 16 and the differences in the formation of the limbs and face, it is not clear in what ways the two could be more similar morphologically. On the other hand, human trisomy 21 is associated with immune defects which, al-

though somewhat difficult to characterize, appear to be related to abnormalites in T-lymphocyte ontogeny and function[40, 50, 95]. In addition, in view of the abnormalities in enzyme activities in trisomy 21 erythrocytes, there may be a defect in erythropoiesis as well. Therefore, it is of considerable interest that mouse trisomy 16 hematopoietic stem cells are quantitatively and possible functionally defective in many respects.

When attempts were made to use fetal trisomy 16 cells for the repopulation of lethally irradiated hosts, it was found that the red cell counts of the resulting chimeras were moderately ($\sim 20\%$) reduced and lymphocytes severely ($\geq 80\%$) reduced[65]. These abnormalities are also reflected by the behavior of trisomy 16 cells in trisomy 16↔2n aggregation chimeras. Unlike most trisomy 16 cell types, which comprise 50–60% in chimeras examined prior to term and 30–40% in juvenile and adult chimeras, there are marked deficiencies of trisomy 16 cells in the blood, spleen, thymus, and bone marrow, particularly in the adult chimeras[27]. These abnormalities are reflected in hematological and immunological abnormalities of the trisomy 16 fetuses themselves[46, 65]. There is a profound hypoplasia of the thymus and spleen, with reductions of $\geq 80\%$ in numbers of thymocytes and spleen cells. However, the pre-B and B-cell populations in the liver are affected much less. Marked reductions ($\geq 90\%$) are present in the proportions and absolute numbers of the granulocyte-macrophage (CFU-C) and primitive erythroid (BFU-E) stem cells, and less severe (50–70%) reductions in multipotential stem cells (CFU-S) and the later erythroid stem cells (CFU-E), all in the liver. The hematocrit is reduced by 50%. Despite the great deficiency of thymocytes, in vitro cultures of thymuses from day 14 fetuses reveal that proliferation and maturation of these cells occur at normal rates. Clearly, there are developmental defects in a large number of stem cell systems in the trisomy 16 mouse fetuses which, as has already been noted, may be of considerable relevance to the human situation.

Work is now proceeding on several aspects of fetuses with mouse trisomy 16 and of trisomy 16↔2n chimeras. These studies include not only the immunological investigations just described, but also analysis of the congenital heart disease and of the development of the brain[22, 91]. The latter is of particular importance since the major adverse consequence of human trisomy 21 is, of course, on the function and presumably the development of the brain. In addition, detailed comparative genetic studies of human chromosome 21 and mouse chromosome 16 are being conducted to establish more precisely the actual degree of homology between the two chromosomes.

## *Conclusion*

Although this article began with a review of human developmental abnormalities, it has ended with a discussion of genetic defects in the mouse. This is probably as it should be. While the ultimate goal of the human developmental geneticist may be to understand both normal and abnormal development in man, man is clearly not the ideal experimental subject, particularly with regard to events occurring during the period of gestation. The mouse, on the other hand, while not having the highly evolved brain, the physiognomy, or the exact genetic constitution of man, does nevertheless share with him overall similarities in genetic organization, regulation and expression, metabolism, and development. Furthermore, the mouse, as well as other organisms not discussed here, has a large number of experimental advantages. Therefore, in the long run the most direct approach to elucidating the genetic problems of human development will involve, as I have illustrated in this article, the study of not only man himself but also of the appropriate experimental models in other species. With the recent and continuing major advances in molecular and cell biology to build upon, human developmental genetics should soon become an exciting and rapidly moving field.

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# The role of somatic cell genetics in human gene mapping

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*Key words.* Cell fusion; cell hybrids; gene transfer; human genome; mapping.

## *Introduction*

Genetics based on parasexual events, like the transfer of genetic material of a different origin into the genome of a proliferating eukaryotic somatic cell and the segregation of donor genetic material from the fusion product, is called somatic cell genetics. Examples of this process are the fusion of somatic cells into hybrids, which can be considered as the transfer of the complete genome from one somatic donor cell to a recipient somatic cell, and also the transfer of isolated nuclei, metaphase chromosomes, genes or arbitrary DNA fragments of eukaryotic or prokaryotic origin into recipient cells. Although this definition does not explicitly exclude gene transfer in vivo somatic cell genetics in the animal kingdom has until recently[123] been almost exclusively a domain of cell culture in vitro.

Cell fusion and gene transfer methodology have developed during the last 20 years into versatile tools which can be used in many fields of biological and medical research. Numerous detailed reviews[31, 39, 41, 44, 96, 110] have followed up this development and can serve to trace both the history and the methodological specificities.

Not only have somatic cell genetics methods and their fields of application proliferated at an exponential rate, but Human Genetics, the specific subject of this issue, has also encountered an explosion of information during recent years since molecular geneticists have learned that the anatomy of the human genome and the functioning of its genes in normal or mutated cells can best be studied in man.

Somatic cell genetics has contributed significantly to our understanding of mutagenesis[9, 117], dissection of human genetic diseases by genetic complementation[5, 31], dosage compensation[124], analysis of malignancy[109, 122], gene expression, and gene regulation[15, 20, 92]. It has even opened up a new era in immunology by providing the methodology for production of hybridomas capable of secreting monoclonal antibodies of predefined antigenic specificity[63]. For the field of human genetics its major success, however, has been in gene mapping.

This review will cover the current application of somatic cell genetics to the analysis of the anatomy of the human genome considering complementary approaches like family studies, in situ hybridization and chromosome sorting. One major task will be to demonstrate how the somatic cell genetics approach can bridge the gap which previously separated by orders of magnitude the mapping resolution of genetics and molecular biology.

## *Sources of information on human gene maps*

Many authors have reviewed the information on human gene mapping in general[39, 49, 56, 74, 99, 106, 108] or on specific fields of application, for instance medical genetics[28, 53, 75, 76, 107], mapping and analysis of oncogenes[17], characterization of gene families[18] or comparative genetics[87]. These reviews offer a digest of the state of the art. A complete collection of available information is compiled by regular Human Gene Mapping Conferences[46–52]. The committee reports of these meetings cover all available published gene mapping data. The material is evaluated using an arbitrary scale of credibility ranging from 'confirmed' to 'in limbo'. In addition to compiling an updated