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Review and Hypotheses: Somatic Mosaicism: Observations Related to Clinical Genetics

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The work of Mary Lyon made us aware that half the human population is functionally mosaic with regard to their X chromosome (Lyon 1961). Normal women are made up of clones of cells, some with an active paternal X chromosome and others in which the maternal X is active. Perhaps it has been living with that reality for the past 27 years, without any apparent ill effect, that has made me comfortable with the concept that we may all be mosaic in other ways as well.

Since the number of cells in the human body (10^{14}) greatly exceeds the denominator of the mutation rate for almost all genetic disorders so far recognized, it seems likely that during the course of embryonic, fetal, and extrauterine life, virtually the entire repertoire of known mutations must occur within all normal individuals, giving rise to areas of somatic mosaicism that result from the clonal expansion of the mutated viable cells that arise during pre- or postnatal life. The mosaicism may result from chromosomal abnormalities (missing or extra chromosomes or parts of chromosomes), from single-gene mutations, or possibly from the incorporation of extrachromosomal DNA. This kind of change may occur as a postzygotic event in a single cell and then be passed on to daughter cells at any time during the development or lifetime of the individual (although a mutation leading to mosaicism could also occur at the half-chromatid stage, before fertilization [Gartler and Francke 1975; Lenz 1975]). The expected effects of somatic mosaicism would depend on a number of factors, including (1) the type of mutation (deletion, point mutation, etc.) that occurs, (2) the type of gene (housekeeping, structural, regulatory, etc.) in which it occurs, (3) the locus (or loci) at which the change occurs, (4) whether the mutation has led to heterozygosity or homozygosity of the mutant or wild-type allele, (5) the specific cell type(s) (and the related tissues and organs) that are involved, (6) the stage in development during which the mutant event occurs, and (7) the fate of the particular cell lineage in which it arose (migration, mingling, selection, etc.).

One would expect very different effects if the mutation occurred in a growing and developing organism, as compared with an end stage–differentiated cell. Recent developments in cancer research suggest somatic mutations are responsible for most, if not all, leukemias, lymphomas, and solid tumors (Le Beau and Rowley 1986). It is against the background of this cancer research that it seems possible for somatic and germline mosaicism to explain a variety of clinical observations as well.

Chromosomal Mosaicism

Chromosomal mosaicism has long been recognized in cultured lymphocytes (as seen for instance in Turner and Down syndromes). Occasionally, fibroblast studies have been necessary to demonstrate the mosaicism (Nielsen et al. 1988). More recently, the presence of a normal set of chromosomes in lymphocytes with mosaicism for a chromosomal abnormality in fibroblast cells has been recognized with increasing frequency among phenotypically abnormal individuals (Pagon et al. 1979; Hunter et al. 1985; Thomas et al. 1986; Turleau et al. 1986; Donnai et al. 1986; Peltomaki et al. 1987). Certain features—such as streaky or patchy pigmentary skin changes, areas of abnormal body growth, generalized undergrowth, asymmetry with unilateral hypoplasia, or even hemihypertrophy in an individual with mental retardation—have been helpful clues to the presence of mosaicism for chromsomal abnormalities. It seems likely that many, if not all, cases previously described as hypomelanosis of Ito represent chromosomal mosaicism (Turleau et al. 1986), perhaps sometimes in tissues not usually cultured for chromosome studies. It may be that some families carry specific

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chromosomes that are prone to anaphase lag or nondisjunction and that thereby predispose them to somatic mosaicism (Juberg et al. 1988).

Some interesting and unexpected types of chromosomal mosaicism have been reported recently, such as confined placental aneuploidy in fetuses who have intrauterine growth retardation and a normal karyotype in their lymphocytes and fibroblasts (Kalousek and Dill 1983). With the advent of chorionic villus sampling, placental chromosomal mosaicism is being recognized to be a fairly frequent finding, occurring in 1%–5% of samples (Lilford et al. 1987) and may be confined to the placenta (Kalousek et al. 1987). This phenomenon is not so implausible as it may seem superficially when it is recognized that at least 95% of the cells of the blastocyst give rise to the extraembryonic structures, including the membranes and placenta (Crane and Cheung 1988). In some cases when the fetus is aneuploid, the presence of a normal cell line in the placenta may even explain why a small minority of fetuses affected with specific chromosome abnormalities are able to survive to term (Kalousek and McGillivray 1987).

Single-Gene Mosaicism

Happle (1986) has suggested that the McCune-Albright syndrome represents a somatic dominant mutation which, if present in all cells of the body, would result in early lethality. Because the gene for McCune-Albright syndrome has not been defined, this hypothesis cannot yet be proved. However, it is a very appealing concept. It seems possible that this mechanism could also account for other sporadic conditions (such as Proteus syndrome, Klippel-Trenaunay-Weber syndrome, Maffucci syndrome, encephalo-cranio-cutaneous lipomatosis, Sturge-Weber syndrome, neurocutaneous melanosis, and Ollier disease) in which there are patchy areas of marked tissue dysplasia. Happle (1987) predicts that in this type of disorder, fetal survival is only possible when the mutation is present in mosaic state and has therefore arisen during development. If the mosaicism involved the germ line, the mutation could be transmitted and be present in many gametes but would probably only be manifested as subfertility or multiple miscarriages, because of the early lethality when the mutation is present in all cells of an embryo. New pulse gel techniques may allow detection of DNA differences between normal and dysplastic tissue in at least some such individuals and thereby allow isolation of the abnormal genes.

Mild manifestations in an individual with an apparent "new" single-gene mutation may represent somatic mosaicism. Maddalena et al. (1987) recently reported a boy with ornithine transcarbamylase deficiency who was very mildly affected and found to have two cell lines; one with a normal X chromosome and the other with a deleted ornithine transcarbamylase gene. Shun-Shin (1954) described an autosomal dominantly inherited condition of radioulnar joint malformation. The condition usually affected both arms. However, the first affected individual in the family (the patriarch of a very large family) had involvement of only one arm while all his offspring had bilateral involvement. This discrepancy suggests that the first affected man had mosaicism involving both somatic and germ-line tissues. Rasmussen and Frias (1988) recently described a family with Pfeiffer syndrome in which the child had typical manifestations while the mother had only involvement of one hand and mild midfacial hypoplasia. Until the genes for these latter two conditions are isolated, proof of mosaicism cannot be achieved. However, it may be that by the comparison of DNA from different tissues in the apparently mosaic parent the genes can be isolated. Thus, very careful physical examination of the parents of an apparent "new" mutation may have a number of benefits. It may be that the concept of anticipation arose from the observation of families in which the first affected individual (generation) represents somatic mosaicism giving milder involvement than usual and thereby suggesting increasing severity in the subsequent generations in which mosaicism is not present.

Germ-Line Mosaicism

Recently, there have been a number of reports suggesting that somatic mutations of the germ line may be present in phenotypically normal individuals. Duchenne muscular dystrophy (Edwards 1986; Bech-Hansen et al. 1987; Darras and Francke 1987; Wood and McGillivray 1988), pseudochondroplasia (Hall et al. 1987), Apert syndrome (Allanson 1986), Crouzon syndrome (Rollnick 1988), osteogenesis imperfecta type II (Byers et al. 1988), tuberous sclerosis (Connor et al. 1986; Hall and Byers 1987), achondroplasia (Bowen 1974; Fryns et al. 1983; Opitz 1984; Reiser et al. 1984), ornithine transcarbamylase deficiency (Brusilow and Valle 1987), hemophilia A (Youssoufian et al. 1987), aniridia (Reed and Falls 1955), and dominantly inherited ectrodactyly (David 1972) have all been reported in families in which parents are phenotypically normal by all known tests but in which more than one of their children have been affected with a dominantly inherited or X-linked recessive disorder. Possible explanations that

have been proposed include genetic heterogeneity (more than one mode of inheritance), epistasis, "premutation," and germ-line (gonadal or germinal cell) mosaicism in one of the phenotypically normal parents. .

Byers et al. (1988) have reported sibships in which more than one child had a lethal dominant form of osteogenesis imperfecta with the same "new" mutation demonstrated in their collagen and were born to clinically normal parents who had only normal collagen in the skin and fibroblasts. Similarly, Bradley et al. (1980) have demonstrated germ-line mosaicism on a biochemical level for a mutation in the beta-globin gene, resulting in hemoglobin Koln. Chilcote et al. (1987) reported a family in which two sibs had the same microscopically visible deletion of chromosome 8, while two other sibs were normal and both parents had normal chromosome studies with regard to lymphocytes and fibroblasts. Women with normal X chromosomes in their somatic cells have been reported who have had two sons affected with Duchenne muscular dystrophy, both sons carrying the same DNA deletion on the X chromosome (Edwards 1986). Grandparents have been reported who have had two affected grandsons, each with the same mutations, through different daughters, although the grandparent him- or herself does not have the mutation in his or her own white blood cells or fibroblasts (Edwards 1986; Bech-Hansen et al. 1987; Darras and Francke 1987; Wood and McGillivray 1988). These findings suggest that phenotypically normal individuals may transmit several gametes that are clonal descendents of a single progenitor cell in which a de novo mutation occurred during the early development of the parent. In other words, it appears that during the embryologic development of the "carrier" parent, a mutation occurred that involved a germ-line cell or its precursors. As there are about 30 mitoses in the germ cells before each meiotic event in the female—and more in the male—it may in fact be that most germ-line mutations are mitotic. Since there are thought to have been over 6 million ova in the combined ovaries of each human female in early fetal life, several ova with mutations for the common genetic disorders would be expected to have been present in the ovaries of every female. However, most germ-line mutations that occur would not be expected to manifest in either the carrier individual or in future generations.

Manifestations of Somatic and Germ-Line Mosaicism

It is interesting to speculate how somatic mosaicism for various specific disorders might be expressed. Work in mice on cell lineage suggests that some embryonic cell lines remain quite separate while others mingle and migrate (West 1978; Gardner 1983). It would be expected that, in a given individual, mosaicism for a specific mutation could be isolated to the germ line or soma or be present in both germ-line and somatic tissues. It is still not clear how the germ line is partitioned off from other cell lines. Work in transgenic mice (Soriano and Jaenisch 1986) and chimeric mice (Mintz et al. 1973) suggests that it may be at a very early stage. However, the situation is much less clear in the human (Luckett 1978; Gardner 1983), and partitioning may occur in a different way. Furthermore, a particular spontaneous mutation, which occurs early and involves both germ-line and somatic cells, may be selected against in some somatic cells that require the gene product for normal growth, while the mutation is tolerated in the germ cells.

In man, the mutation for neurofibromatosis can present as a "segmental" abnormality in which only one part of the body is affected with neurofibromatosis—and usually in a relatively minor way. It is known that in this situation the parents of the affected proband are invariably normal, and in those cases in which the gene is transmitted to the offspring of an individual with segmental neurofibromatosis, the usual neurofibromatosis I phenotype (i.e., nonsegmental) is observed (Riccardi and Lewis 1988). This suggests that the individual with segmental neurofibromatosis represents a somatic mutation involving a patch of somatic cells—but sometimes germ-line cells as well.

The mutations that have been characterized in osteogenesis imperfecta type II are sufficiently severe that they would be lethal if present in all bone-forming cells of the parent and are probably only tolerated in the carrier parent when the clone that carries the mutation either has been overgrown by normal cells, is present in cells that do not normally express the gene for type I collagen, or is present in a tissue in which this type of collagen is not essential, such as germ cells and gonad cells (Byers et al. 1988).

In some cases the carrier parent may show "microforms" of the disorder. For instance, in psuedoachondroplasia the presumed mosaic parent with two or more affected children may demonstrate very mild manifestations of the disease (e.g., short stature in one family and limitation of elbow extension in another family) (Hall et al. 1987). Depending on the type of mutation, the gene affected, the time in development, the number of cells involved, the tissue types affected, and the particular cell lineage, the phenotypic manifestations of mosaicism in the carrier could be no effect at all, a gener-

alized effect (ranging from mild to severe), or a segmental, streaky, or patchy effect.

Work in mice with spontaneously mutable genes (Searle 1978), in transgenic mice (Soriano and Jaenisch 1986; Gridley et al. 1987), and in chimeras derived by cell mixing (Mintz et al. 1973) and from pluripotential stem cell–line transplantation (Robertson 1986), as well as the use of nontoxic dyes to tag single cells (Kimmel and Warga 1988), may give sufficient insight into cell lineage and cell interactions during embryonic development to make predictions of recurrence risk possible in the future.

Identification of fathers who have germ-line mosaicism may be possible, in the not too distant future, by DNA analysis of sperm. The demonstration of a heterozygous pattern in the DNA from sperm (or possibly even ova) from an individual who shows a homozygous normal pattern in skin fibroblasts or blood lymphocytes would provide strong presumptive evidence for germ-line mosaicism and might even permit the reliable estimation of a recurrence risk.

In disorders with chromosome breakage—e.g., Fanconi anemia—the frequent but unpredictable presence of congenital anomalies may reflect additional mutations arising during development, owing to chromosomal breakage. The congenital anomalies in Fanconi anemia seem to have a more consistent pattern than those seen in Blackfan Diamond patients. Perhaps this reflects times during development or tissues that are more susceptible to mutations. Cytogenetic and DNA studies of affected tissues may demonstrate consistent change, in addition to the nonspecific breakage seen in these patients.

It may be important to consider both whether germline and somatic mutations differ with respect to the proportion that is due to chromosome deletions versus single base changes and whether the paternal or maternally derived chromosome is more likely to be involved. The data that are accumulating on Duchenne muscular dystrophy, the hemophilias, and retinoblastoma may be of help in defining whether there are differences in the frequency of these events in germ cells and somatic cells. Recent data from van Ommen's (den Dunnen et al. 1987) group suggest that more than 50% of cases of Duchenne muscular dystrophy are due to chromosome deletion. Other data from Duchenne families suggest that at least 5% of mutations arise as germ-cell mosaicism in the mother or grandfather (Edwards 1986; Bech-Hansen et al. 1987; Darras and Francke 1987; Wood and McGillivray 1988). Other genes may have very different ratios. The mechanisms leading to mutations in meiosis are likely to be different from the mechanisms leading to mutations in mitosis, and the risk of recurrence for the family therefore may be different in the two situations.

Recurrence Risk

Unfortunately, the data available on single-gene "new" mutations from the disorders so far characterized on a biochemical or DNA level suggest that many (e.g., over 5% of cases) of what appear to be "new" mutations may actually represent a substantial parental germline mosaicism (Bech-Hansen et al. 1987; Darras and Francke 1987; Hall and Byers 1987; Hall et al. 1987; Byers et al. 1988). One implication is that there may be a real risk for recurrence after an apparent dominant mutation in what had previously been thought to represent a risk-free situation. It seems likely that new mutations associated with advanced paternal age represent mitotic or meiotic errors occurring during germ-cell proliferation that are less prone to be associated with extensive clonal mosaicism than is germline mutation arising during the father's intrauterine development. However, this correlation has not yet been made, and new mutations associated with advanced paternal age may not be recurrence-risk free, either. So despite the plausibility of this assumption, it remains to be established whether the age-related "new" mutations—and which ones—are in fact associated with a very low recurrence risk.

Based on clinical observations (which may only reflect bias of ascertainment), there seem to be two subgroups of disorders with regard to risk of recurrence in what appears to be a "new" dominant mutation: (1) a group, including achondroplasia and neurofibromatosis, with relatively low empiric risk of recurrence and (2) a group, including pseudoachondroplasia and tuberous sclerosis, with relatively higher empiric risk of recurrence. Once DNA markers are available in these disorders, more accurate risk estimations can be made and those structural differences in the genes (e.g., size, position on a chromosome, etc.) that make them more or less susceptible to mutation may be determined. In addition, a distinction between maternally derived and paternally derived mutations may reflect different mechanisms (such as the effect of advanced paternal age on spermatogenesis or a possible protective effect from methylation of DNA).

The role of germ-line mosaicism in the occasional unexpected aggregation of diseases is difficult to assess. During the past 3 decades, a vast array of sometimes

ill-defined genetic syndromes have been described which have been attributed to recessive inheritance *solely because* there had been observed recurrence of a second affected child to parents who are themselves phenotypically normal. In addition, genetic heterogeneity (different forms of a disorder—both autosomal dominant and autosomal recessive inheritance) have been suggested purely on the basis of pedigree analysis (Hall 1975), even though no physical, pathologic, or radiographic distinction has been demonstrated. Although such presumed autosomal recessively inherited traits are usually quite rare, they are often not demonstratively associated with parental consanguinity. Thus, it seems reasonable to suggest that some of the traits without the expected proportion of consanguinity which exhibit "horizontal transmission" may be attributed to germ-line mosaicism (or even to strictly environmental influences).

These considerations must give the clinical geneticism pause for concern when providing information to families seeking genetic counseling regarding recurrence-risk figures. Both the risk of recurrence of an apparent new mutation and the chance that the affected individual who has been thought to have an autosomal recessive trait will himself have an affected child must be reevaluated.

The Time in Development When a Mutation Arises

One would anticipate that the effects of somatic mutation of either genes or chromosomes would vary with both the time during development at which the mutation occurs and the particular cell involved. For instance, in an embryo, a clone of mutated cells might result in malformations of an involved structure (Gridley et al. 1987). In the embryo, "programmed" cell death normally occurs, "sculpturing" various structures; a mutation in cells destined to die could have no effect because the cells die off, or it could lead to their continued survival when in fact they should have died—and thus to a malformation on that basis (Gardner 1983). In the fetus or infant, a clone of cells with a particular mutation might lead either to positive or negative growth, to differentiation or development of a specific area (or segment or tissue), or to the failure of structure to regress in the normal manner. After growth and development are complete, the most common manifestations of mosaicism for a new mutation are likely to be malfunction (as in aging) or overgrowth (as in neoplasia). All adults have various growths such as moles and benign tumors, and almost a third of people die from malignant disorders that probably arise as random somatic mutations. Recent developments in cancer research have clearly defined this type of change on a molecular level (Murphree and Benedict 1984; Cavenee 1986; Le Beau and Rowley 1986).

Cases of hemiatrophy and hemihypertrophy may well represent mosaicism for a single gene or for a chromosomal mutation—or even for a whole set of chromosomes, as in the case of diploid/triploid mosaicism (mixoploidy) (Jenkins et al. 1971). Since somatic mosaicism of extra chromosome(s) in hemihypertrophy has been demonstrated, it can be anticipated that mosaicism for a single gene could also produce hemihypertrophy or hemiatrophy. Deficient or excessive growth are known to affect segments, quadrants, or the whole body. If these growth abnormalities are due to somatic mutation, then they would be expected to reflect cell lineage patterns in humans. The occurrence of Wilms tumor is known to be strongly associated with hemihypertrophy (Hoyme et al. 1986). However, an important and relevant question is why Wilms tumor does not develop in all patients with hemihypertrophy. The work of Wilms tumor suggests imprinting may even play a role (Wilkins 1988). Wilms tumor is known to occur with loss of the maternal chromosome 11. One could hypothesize that only in those cases of hemihypertrophy in which the underlying mosaicism involves the relevant part of chrosome 11 and in which the appropriate renal tissue is involved will there then be a predisposition to develop Wilms tumor. Increased or decreased growth (of a tissue, a body part, or the whole body) could be the effect of a mutation at either a growth-factor locus (or oncogene locus) (Adamson 1983), of a growth-factor receptor that directly affects that particular tissue or of a change that affects the response to circulating levels of growth factors (Fialkow et al. 1987).

Tissue Tolerance and Growth

Depending on the particular tissue and mutation, some chromosomal anomalies and single-gene mutations may be lethal to the cells and others may be tolerated if they do not have a severe effect on that tissue, while still other mutations may actually have a selective advantage, as in the case of malignancies (Fialkow et al. 1987). Observations on patients with trisomy 8 mosaicism and tetrasomy 12p mosaicism would support this concept, since mosaicism for these aneuploidies appears to be much better tolerated in fibroblasts than in lymphocytes (Niss and Passarge 1976; Hunter et al. 1985; Pel-

tomaki et al. 1987). When a gene is required for cell survival, the presence of an abnormal gene may lead to selection against that cell population. In the case of X-linked disorders, selection against maternally or paternally derived active X-bearing cells indicates that this type of selection occurs regularly. The observations that severe mutations of the Lesch-Nyhan locus fail to give intermediate enzyme levels in the red blood cells of female heterozygotes but do express intermediate levels in fibroblasts (Migeon 1970; Strauss et al. 1981), and the observation that in patients with incontinentia pigmenti the cells only survive in certain tissues if they have inactivated the maternally derived X carrying the incontinentia pigmenti gene (Migeon et al. 1987), provide strong evidence that mutant cells for various loci may survive in some tissues and not in others, based on in vivo selection. The recent work on X inactivation in carriers of X-linked immune deficiencies also supports the concept of selection for only normally functioning B and T cells (Goodship et al. 1988).

In dominant lethal disorders normal cells may occasionally arise (by back-mutation, gene conversion, mitotic crossover, or double mitotic nondisjunction), and these normal cells may then outgrow the mutant cells, interspersing themselves throughout the developing body and allowing survival of what would otherwise be a lethal condition in a human; such may be the explanation for the occasional survival of males with X-linked incontinentia pigmenti (Hecht and Hecht 1983) and Melnick-Needle syndrome (Donnenfeld et al. 1987; Krajewska-Walasek et al. 1987).

Somatic mosaicism potentially allows isolation of genes that are normally lethal in humans, since, by definition, if present in all cells, a lethal mutation would not allow survival to term and might not even be identified among human spontaneous abortions. In *Drosophila* and mice, dominant disorders manifesting as heterozygotes are often lethal in the homozygote. Conditions such as McCune-Albright syndrome may well represent lethal human mutations when present in all cells, but, by isolating the tissue involved, it may be possible to compare the DNA from involved tissue with DNA from patches of normal tissue to search for relevant differences. It may also be possible to use probes for lethal conditions isolated from lower animals and to find similar changes in the patches that represent lethal human genes. Areas of such tissue dysplasia as hemangioma, bony dysplasia, and ectopic tissue are likely to be rich sources of somatic chromosomal or single-gene mutation.

Development of Homozygosity in Peripheral Tissues

One would expect some other types of effects from the possibility of somatic mosaicism. Murphree and Benedict (1984), Cavenee (1986), and Scrable et al. (1987) have described six possible mechanisms: (1) mitotic nondisjunction and loss, (2) nondisjunction and reduplication, (3) mitotic recombination, (4) localized gene conversion, (5) point deletion, or (6) point mutation, whereby a mutation in—or deletion of—the retinoblastoma gene leads to the absence of all normal alleles. One would anticipate that those same mechanisms could lead to homozygosity or hemizygosity at other loci. Uniparental disomy has recently been demonstrated to be another mechanism responsible for homozygosity of the cystic fibrosis gene (Spence et al. 1988), and it seems likely that rare mitotic errors could produce mosaicism for the presence of uniparental disomy involving any chromsome (Warburton 1988)—and, consequently, any gene. Therefore, it seems very possible that, in a carrier of a dominant gene, patches of tissue might occur that represent areas that have become either homozygous for the dominant gene or homozygous normal. There are examples of this in *Drosophila* and mice (Postlewait 1978; Searle 1978; West 1978). The expectation that such areas do occur may account for some of the patchy dysplasias and unusual malformations and anomalies seen occasionally and unpredictably in dominantly inherited disorders. For instance, areas of bony dysplasia are seen frequently in neurofibromatosis, and patchiness is seen on muscle biopsy in a variety of myopathies. Patchy dysplasia or areas of increased severity may indicate that the tissue has become homozygous for the abnormal gene. Gardner et al. (1988) have suggested that the somatic mutation to homozygosity is the explanation for an area of severe involvement in one member of a family with familial ectopic ossification. Once linkage or gene isolation has been achieved, it may well be possible to test this hypothesis.

Carriers for some recessive disorders, such as Fanconi anemia and ataxia telangiectasia, are said to have an increased risk of cancer (Swift et al. 1974). This has been thought possibly to relate to chromosomal instability or increased levels of abnormal metabolites in the carriers, but it may also be related to areas in their bodies that have become homozygous by either somatic mitotic crossover events or chromosome breakage.

The mechanisms seen in retinoblastoma and unipa-

rental disomy suggest further that single-gene defects, both dominant and recessive, could actually correct themselves. A possible example of somatic mosaicism involving back mutation to the normal allelomorph is the remarkable patient, reported by Rimoin and McKusick (1969), who had classical achrondroplasia with several normal fingers.

The real question is whether we know enough to predict what somatic mosaicism would look like in different conditions and in different tissues—or how often it will involve both somatic tissues *and* germ-line cells or only germ-line cells. Can we predict what *mosaic* homozygosity will look like for dominant conditions? We know that the patient with homozygous achondroplasia (Hall et al. 1969) and homozygous Osler-Weber-Rendu Syndrome (Snyder and Doan 1944) is more severely afflicted than the heterozygote, while in Huntington disease the homozygote appears to be indistinguishable from the heterozygote (Wexler et al. 1987). Few other examples of homozygosity for dominant genes have been described—and certainly not in mosaic form. When specific genes are mapped or sequenced, it may be possible to compare tissues and their involvement.

Conclusions

Mosaicism is a pervasive phenomenon that almost certainly affects all large multicellular organisms. When expressed in somatic cells, mosaicism can be an important cause of neoplasia and, possibly, of other aspects of the aging process. Somatic mosaicism can also be an important and sometimes dramatic cause for phenotypic variation in the expression of genetic traits. Germline mosaicism can lead to familial aggregation of affected individuals and provides an important explanation for the recurrence of rare mutations within a single family. In the past, only in the case of chromosomal abnormalities has it been possible to confirm the existence and significance of mosaicism; but the development and application of molecular genetic techniques have now provided many exciting approaches for identifying and analyzing a much wider range of mosaic states in human beings.

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