Genetics in Heart Diseases

Kwan S. Chang

Individuals vary considerably in their genetic makeup and therefore, being biological potential. Everyone of our genes is presented with thousands of opportunities for mutation. In fact, it was disclosed that independent isolates of the same gene will often display variation in DNA sequence. In any such comparison, 1 in every 200-500 base pairs will vary between two samples. Because of the thousands of base pairs among a single gene, each gene is likely to be found in several versions if it is examined at the level of DNA sequence. Most of these variations appear to be clinically meaningless, however, others can be serious and even life threatening (White 1984).

A vast array of genetic information is coded and packed in DNA. It was shown that genes are integrated into chromosomes and that chromosomes undergo duplication and segregation either mitotically or meiotically prior to cell division (Albert and Sternglanz 1977). The genes themselves are represented by sequences of nucleotides that are located at fixed regions of the chromosome. The DNA part of the chromosome replicates in a semiconservative manner. In this process, the duplex molecule unwinds and each polynucleotide strand serves as the template for synthesis of a complementary strand. The transmission of genetic information is thus explained at the molecular level (Watson 1976). Structurally, these genes are almost DNA, encoding during semiconservative replication. The DNA polymerases that catalyze the replication of DNA contain built-in 3′→5′ exonuclease activities to proofread the progeny DNA molecules and correct mistakes made during the initial polymerization reaction. Mechanisms have thus evolved to facilitate the faithful transmission of genetic information from generation to generation. Nevertheless, mistakes or changes in the genetic material occur. Such sudden, heritable changes in the genetic material are called mutation. The mutation presents genotypic changes including changes in chromosome number (eupeuoidy and aneuploidy), gross changes in the structure of the chromosome (chromosome aberration) and changes in individual genes (Drake 1973).

A fundamental issue in human genetics is the influence of genotype on disease predisposition. Which aspects of phenotype are encoded in genotype and similarly, what are the effects on phenotype of specific changes in genotype? We know only those specific changes that cause the obviously inherited diseases such as Duchenne muscular dystrophy, Huntington's disease and retinitis pigmentosa. We suspect many others such as cancer, heart diseases, Alzheimer's disease and psychiatric disorders, etc.

Another fundamental concept is the notion of genetic components, as opposed to a genetic cause, of a disease. Many of the most interesting human genetic disorders are those that have incomplete penetrance, that is, the presence of a given genotype is not sufficient to cause appearance of phenotype. For example, in Wilms' tumor, the inheritance of a mutant allele will result in the appearance of a kidney tumor only 65% of the time; thus, some factors in addition to the mutant gene are required.

Furthermore, an inherited genetic component may not even be necessary for the development of the disease. Inheritance of a single mutant allele of the retinoblastoma gene is usually sufficient to cause the appearance of the tumor; however, almost 50% of the retinoblastoma cases are thought to be due not to inheritance of a mutant gene but to mutation of somatic cells during development. Moreover, in both instances, somatic loss of a chromosome carrying the normal allele can be an additional component in the occurrence of the disease. Thus, although the genetic component of a disease must, when present, be strongly predisposing, it is often neither necessary nor sufficient for the development of the disease.
Given a specific genotype, environmental components may also be required to reveal specific phenotypes. For example, the symptoms of the porphyrias often appear only when environmental factors such as alcohol, estrogen or iron interact with the genotype (Kappas et al. 1983).

**CONGENITAL HEART DISEASE**

It has been estimated that 3.5% of all pregnancies end in a recognizable chromosome abnormality. By the time when the abortion takes its toll, the number of chromosome abnormalities may be reduced to 0.5% of live births. Recent studies indicated that the prevalence of structural congenital heart defect in live born infants is 3.7/1000, somewhat less than the previous studies (5.5 to 8.6/1000). Among them, 12% of all the infants with congenital heart defect were found to have chromosome abnormalities (Ferencz et al. 1985).

The congenital heart defect has been thought to have multifactorial origins with genetic and environmental influences although familial traits have been stressed on virtually all forms of congenital heart defect (Fraser and Hunter 1975). Monogenic inheritance with autosomal recessive dominant transmission has been postulated (Miller and Smith 1979). Although the overall sibling occurrence rate for all types of congenital heart defect was similar to that previously reported (1.8%), there was a marked increase in the rate of obstructive lesions of the left heart. The familial trait of obstructive defect of the left heart was 4-6 times higher (Table 1).

<table>
<thead>
<tr>
<th>Category of disordered cardiac embryonic mechanism</th>
<th>Sibling (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell migration abnormality (conotruncal)</td>
<td>0/1</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>0/24</td>
</tr>
<tr>
<td>Transposition of great arteries</td>
<td>0/8</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>0/22</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>0/1</td>
</tr>
<tr>
<td>Type B interrupted aortic arch</td>
<td>VSD (type I, supracristal, malalignment)</td>
</tr>
<tr>
<td></td>
<td>0/2</td>
</tr>
<tr>
<td>Flow lesions</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic left-heart syndrome</td>
<td>5/38(13.5)</td>
</tr>
<tr>
<td>Coarctation</td>
<td>3/37(8.1)</td>
</tr>
<tr>
<td>Aortic stenosis, valvar</td>
<td>0/12</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>1/9(11.1)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1/13(7.7)</td>
</tr>
<tr>
<td>Secundum atrial septal defect</td>
<td>1/31(3.2)</td>
</tr>
<tr>
<td>Pulmonic stenosis, valvar</td>
<td>3/33(9.1)</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>0/8</td>
</tr>
<tr>
<td>VSD (type II, membranous)</td>
<td>5/86(5.8)</td>
</tr>
<tr>
<td>Cell death</td>
<td></td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>0/10</td>
</tr>
<tr>
<td>VSD (type IV, muscular)</td>
<td>0/9</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular canal</td>
<td>0/10</td>
</tr>
<tr>
<td>VSD (type III, canal type, inlet)</td>
<td>0</td>
</tr>
<tr>
<td>Targeted growth</td>
<td></td>
</tr>
<tr>
<td>APVR, total</td>
<td>0/12</td>
</tr>
<tr>
<td>APVR, partial</td>
<td>0/1</td>
</tr>
<tr>
<td>Single atrium</td>
<td>0/1</td>
</tr>
<tr>
<td>Other</td>
<td>1/37(2.8)</td>
</tr>
</tbody>
</table>

APVR, Anomalous pulmonary venous return: VSD, ventricular septal defect.


Isochromosome formed by misdivision of a chromosome. Inversions arise when two breaks occur in a single chromosome and the segment between is inverted. The order of the gene is disarranged; however, since none of the genes are lost or duplicated, the carrier of inversion is usually phenotypically normal (Fig. 1). Inversions are frequently found in chromosome No. 9. The most striking and common chromosome abnormalities are trisomies 13 and 18 at 90-100%. The intermediate frequencies are trisomy 21, partial short arm deletion of chromosome No. 4 (4p-) and partial long arm deletion of No. 18 (18q+) at 40-50%. While less common frequencies are reported in partial short arm deletion of No.5 and 45X Turner's syn-

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Trisomy 21 (47, +21; Mongolism, Down's Syndrome)

The abnormal features of Trisomy 21 syndrome include typical dermatoglyphics, reduced acetabular angle, disturbances of tryptophan metabolism and immature polymorphonuclear leukocytes. Other variable traits are third fontanelle, deformed middle phalanx of the little finger, Brushfield spots and an abnormal alimentary canal and lungs.

Heart: Cardiac malformation in this syndrome varies from 39-71%, depending on the authors and also on whether the methodology of examination is clinical or autopsy. However, a report from the Hospital for Sick Children in Toronto estimated about 40% among 174 mongoloids. The common cardiac anomalies are ostium atroventricular commune, ostium primum and persistent atroventricular canal (Lev and Kaveggia 1960). These septal defects constitute over three-quarters of heart malformations. Other abnormalities include patent ductus arteriosus and aberrant right sub-clavian artery (Evans 1950). Generally, cyanotic lesions are less common, although 42 cases of Tetralogy of Fallot have been reported (Tandon and Edward 1973). In addition, 15 cases of transposition were in the medical literature (Hamback et al. 1956). It is estimated that about 70% of the mongoloids with heart anomalies will die after the first month of life. Similarly, two-thirds of the mongoloids who die the first year of life are found to have cardiac malformations. These data are of importance to the family in knowing whether a heart defect is present or absent in a particular mongoloid infant. The incidence of mongolism rises about 30% as the maternal age approaches 40 years (Oster 1953).

Genetics: Non-disjuction is responsible for most
cases of Trisomy 21. The majority of patients are born to older mothers (Carter and McCarthy 1951) and paternal age is irrelevant. It is speculated that X-irradiation (Alberman et al. 1972) is considered to be a causative agent (Rundle et al. 1961; Robinson and Puck 1966).

Trisomy 18 (47, +18; E. Syndrome, Edward Syndrome)

A syndrome of multiple congenital anomalies caused by an extra chromosome in the E group was described independently by two groups of investigators (Smith et al. 1962; Edward et al. 1960). Subsequent reports confirmed their observation (German et al. 1962; Warkany 1966). The clinical features are now almost as familiar to pediatricians as those of mongolism. Small delicate facial features distinguish these patients from other trisomies. The chief signs are low birth weight for gestational age, scaphocephaly, low set malformed ears, micrognathia, non-fixed flexion deformity of the fingers, deformed feet, spasticity and mental retardation. A number of anomalies including renal, gastro-intestinal and skeletal occur less uniformly.

Heart: The rate of cardiac defect is 100% in almost all cases (Kurien and Duke 1968).
defect is the more common anomaly. This is, however, frequently associated with patent ductus arteriosus and atrial septal defect. Aneurysmal transformation around a ventricular septal defect has been observed in partial trisomy (Chester et al. 1970). A high incidence of bicuspid semilunar valves are recorded in literature and moderate degree of aortic and pulmonary stenosis has been described (Townes 1962; Holman 1963). Only occasionally does coarctation of the aorta, transposition of great vessels and A-V canal defect or mitral atresia occur in association with a ventricular septal defects (Scarpa and Borgaonkar 1966). Endocardial fibroelastosis has been the subject of several reports (Lewis 1964). Undoubtedly, cardiac anomalies contribute significantly to the early death of these patients (Surana et al. 1972).

**Genetics:** The incidence of disorder is about 1:4000 births. Females preponderate and the sex ratio is 4:1. The chromosome involved is identified as No. 18 (Smith et al. 1960). Identification by amniotic fluid cell culture at 16 1/2 weeks that was subsequently confirmed at 20 weeks after induced abortion has been reported. The fetus had atrial and ventricular septal defects and bicuspid aortic valves (Hsu et al. 1973). Translocations are rare and give rise to a trisomy syndrome.

**Trisomy 13 (47, +13; D Syndrome, Patau’s Syndrome)**

A syndrome of multiple congenital anomalies associated with an extra chromosome D group was first reported by Patau and associates (Patau et al. 1960). Low birth weight with associated mental retardation, seizures and deafness are common features. Cleft lip, palate and polydactyly are the most striking anomalies, occurring in 75% of the patients. Occular deformities include coloboma, cataracts and anophthalmia. Flexion deformities of the hands, ear deformities and renal tract anomalies have been reported. Capillary hemangioma on the forehead is common. There is abnormal elevation of fetal Hgb F and polymorphic nucle leukocytes have nuclear projections 12 times more frequent than normal.

**Heart:** Over 80% of patients have cardiac anomalies. Transposition of great vessels, truncus arteriosus, atrial septal defect, dextroposition and ventricular septal defect have presented as single defects. Among them, ventricular septal defect, patent ductus arteriosus and atrial septal defect have been commonly encountered (Smith et al. 1963).

**Genetics:** The incidence of trisomy 13 is in the order of 1:7000 to 1:14500. Trisomy of chromosome 13 was first distinguished from other D group chromo-

somes by autoradiography. Mosaics are not infrequent at about 5-10% (Green et al. 1968). Translocation occurs in about 20% of cases in contrast with about 5% of mongolism (Taylor 1970; Erkman 1965). This is most often of the t (13q Dq) constitution. The outlook for these patients is poor. The average life span is about 100 days and about half of those afflicted die during the first month. It is surmised that cardiac anomalies contribute a great deal to their demise, although others feel aspiration from cerebral abnormality may be the major cause of death. Renal agenesis, polycystic kidney and hypoplastic kidney are additional factors contributing to the grave outlook.

**Short-Arm Deletion of Chromosome No. 4 (4p; Wolf Syndrome)**

The 4p-syndrome was initially grouped with 5p- because these patients were considered to have short arm deletion of B chromosome (Wolf et al. 1965). In 4p-syndrome, the associated malformations are complex and the degree of mental retardation is severe. The face is distinctive with disturbance of midline fusion. Prominence of the glabella and cleft palate are common. Deformity of the iris, hypertelorism, misshapen nose, preauricular skin tags, hypospadias and hypoplastic dermal ridges are common clinical features.

**Heart:** Congenital cardiac anomalies in 5p-are as high as 50%. Atrial septal defect of the secundum type (Guthrie et al. 1971), endocardial cushion defect (Arias and Passarge 1970), ventricular septal defect and patent ductus arteriosus are the most common cardiac anomalies. Cases with dextrocardia (Taylor et al. 1970), hypoplastic left ventricle, pulmonary stenosis, bicuspid aortic valve and left superior vena cava have also been reported.

**Partial Long Arm Deletion of Chromosome No. 18 (18q; Carpent Syndrome)**

This rare syndrome was first described by de Grouchy and associates (deGrouchy et al. 1964). It is characterized by growth failure, mental retardation, mid face dysplasia and carp mouth. Although roughly 50% of the patients have congenital heart diseases (Wertelecki and Gerald 1971), detailed information about the cardiac abnormality is scanty. Atrial septal defects with or without mild pulmonary valve stenosis were rarely reported (Curran et al. 1970). At least two cases of ventricular septal defect were also in the literature. In general, the cardiac defect, when present, is usually simple and does not influence on prognosis.

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Short-Arm Deletion of Chromosome No. 18 (18p-)

This congenital abnormality produces an extremely variable phenotype which is severe on some patients but mild on others (Uchida et al. 1964). Cardiac malformation, if present, is usually mild and not a subject for much emphasis.

Ring Chromosome No. 18 r (18)

Since both ends of the chromosomes are lost during ring formation, the clinical consequence might be expected to resemble the effect seen in both 18p and 18q. The cardiac anomalies were described as persistent ductus arteriosus or ventricular septal defect. Also, venous abnormalities have been reported such as the left superior vena cava draining into the left atrium and pulmonary venous return to the coronary sinus (Gropp 1964; Palmer 1967; Wald 1969).

Long-Arm Deletion of Chromosome No. 13 (13q-)

A few cases of loss of part of the long arm of a D chromosome have been reported (Bain and Gauld 1963; Sparkes 1967; Opitz, 1969), which was identified as chromosome No. 13 by autoradiography. Cardiac anomalies were difficult to define because of scarce data, however, two patients with Tetralogy of Fallot and ventricular septal defect were described.

XXY Abnormality (Klinefelter's Syndrome)

This syndrome indicates male phenotype with atrophic male genital organs, mental retardation, and gynecomastia with increased urinary gonadotropin excretion (Klinefelter et al. 1942). Eighty percent of the patients are chromatin positive and have 47 chromosomes with mainly XXY.

Heart: The cardiac anomalies are probably 4-5 times more frequent than the general incidence. A wide variety of malformations were described but Tetralogy of Fallot may be one of the most common anomalies. Among others, Ebstein's anomaly of tricuspid valve, atrial septal defect, ventricular septal defect, aortic stenosis and arteriovenous fistula have been reported.

Monosomy (Turner's Syndrome)

These patients have an extensive number of anatomic abnormalities and failure to achieve secondary sex characteristics at puberty that include short stature, absence of breast development, small amount of pubic and axillary hair, webbing of neck and cubitus valgus (Turner 1938). These women have raised urinary gonadotropin excretion and replacement of ovaries by fibrous tissue. In addition, 80% of the patients have broad chest, congenital lymphedema, low posterior hairline, prominent ears, narrow high arched palate, abnormal nails and small mandible (Lemili and Smith 1963).

Heart: Although cases of coarctation of the aorta were not mentioned by Turner, this anomaly was reported by others (Albright et al. 1942). Much later, the frequent association of heart defects was emphasized (Haddard and Wilkins 1959). In a review of 55 cases of Turner's syndrome, 8 cases of adult type coarctation of the aorta were noted. Among them, 2 cases had additional subaortic stenosis. Nora and associates (1974) examined 40 patients and disclosed that 16 were 45X and 11 had coarctation of the aorta, 4 were 45X/46XX mosaics and all had pulmonary stenosis, 16 were 46 XX and 14 of these had pulmonary stenosis, and 4 were 46 XY and 3 of these had pulmonary stenosis and 1 aortic stenosis. The confusion was due to inclusion of the patients with what is now generally referred to as the Noonan syndrome (Rainier-Pope et al. 1964). Thus, there were two main groups of cardiovascular anomaly; coarctation of the aorta was present in 70% of patients with heart disease and 45X constitution but not in the mosaics with Noonan syndrome. Pulmonary stenosis with or without atrial septal defect was present in 90% of the patients with the Noonan syndrome or with the mosaic Turner's syndrome but never in the true 45X Turner's syndrome with heart disorder. The clinical consequence is that if a patient with apparent Turner phenotype is found to have pulmonary stenosis, one can confidently assume that the chromosomal arrangement will not be 45X. On the other hand, if the patient has coarctation of the aorta, she cannot have pure 46XX and there is an extremely high probability that she will have 45X constitution. The high frequency of renal anomalies in Turner's syndrome, 12 of 30 patients studied by Bishop and associates in 1960, suggest that systemic hypertension in 80% of the patients would probably be of renal origin. (Engel and Forbes 1965).

Genetics: There has been a considerable debate over which patient should be labeled as having Turner's syndrome and when within a group of phenotypically similar patients, one withdraws from the classic definition and assigns another name to the disorder. The English workers have, for years, considered Turner's syndrome to be very strictly only these patients having the clinical features described by Turner himself such as infantilism and webbing of the neck.
ty four percent of such patients have 45X constitution and 6% are mosaic 45X/46X (Polani 1968). A second
group of patients with the same phenotype but without webbing of the neck have been labeled ovar-
ian dysgenesis. Half of these patients have 45X while one-quarter are mosaic and another quarter have
structural chromosome anomalies such as deletion or isochromosomes (Polani 1969). The phenotypic vari-
ation of Turner's syndrome thus appears to be the result of sex chromosome mosaicism deletion or a
combination of both (Ferguson-Smith 1965; Ullrich 1949). Other patients with short or normal status, and
or without neck webbing and other somatic abnor-
malities but with normal ovarian function and 46XX
constitution without mosaicism, have been labeled
as having Bonnevie-Ullrich syndrome (Mckusick 1972).
A group of males with a similar phenotype have been
termed as having Turner's Syndrome in the male if
the patient had abnormal sexual development or
Bonnevie-Ullrich syndrome in the male if there was
no sexual abnormality. American investigators have
recently preferred to make the separation of Turner's
syndrome from Turner simulating conditions by the
Karyotypic approach and have Ullrich and Male Turn-
er's syndromes for the moment with another inclu-
sive eponym, the Noonan syndrome (Noonan and

HYPERTROPHIC CARDIOMYOPATHY

Teare first reported the genetic trait of hypertrophic
cardiomyopathy in his initial description of disease
in 1958. This observation was followed by several ear-
ly reports of single pedigrees in which clinically overt
hypertrophic cardiomyopathy was identified in sub-
sequent generations in a pattern consistent with au-
tosomal dominant inheritance (Walther et al. 1960;

Applications of echocardiography to cardiac dis-
ease in the early 1970s have made major advances
in diagnosis and confirmed the impression of an earlier
single pedigree trait, that the hypertrophic cardi-
omyopathy is often genetically transmitted in a pat-
tern consistent with an autosomal dominant trait
(Clark et al. 1973; Tencate et al. 1979; Kishimoto et
al. 1983; Branzi et al. 1985). However, the frequency
of cardiac abnormality has been a subject of con-
troversy ranging from 60% to 90%. These discrep-
ancies may be attributable to several factors including
differences in the selection of probands, precise criter-
ia and methods of study. However, improvement has
been made by rapid advances in the technical and
interpretative capability of echocardiography that
now permit greater accuracy in assessing the left ven-
tricular wall thickness and thereby minimizing the false
positive diagnosis of hypertrophic cardiomyopathy.
In particular, the application of real time two dimen-
sional echocardiography can afford greater accuracy
in defining the right and left surface of the ventricu-
lar septum. Also, it should be pointed out that any
echocardiographic search for hypertrophic cardi-
omyopathy in children may overlook the diagnosis
because the hypertrophic ventricular pattern may de-
velop de novo during childhood and may not have
yet appeared at the time of any single echocardi-
ographic evaluation. In fact, the morphologic expres-
sion of genetically transmitted hypertrophy shows
greater variation and marked dissimilarities are usually
evident among closely related persons (Maron et al.
1986). The variation in the distribution and pattern of
left ventricular hypertrophy may be just as great be-
tween related members of the same family as be-
tween unrelated patients in different families. It is
speculated, therefore, that the dissimilar morphologic
expressions in first degree relatives reflect variations
in the expression of a signal gene, although these
different phenotypes could imply that inheritance is
mediated by more than one gene at different loci (Ciro
et al. 1983). The significance of the non-familial sporad-
ic form of hypertrophic cardiomyopathy is uncertain.
Some sporadic cases could, in fact, be of a genetic
nature and represent a new mutation or autosomal
recessive transmission. On the other hand, the sporad-
ic cases may represent an etiologically distinct new
disease that appears to be similar phenotypically to
typical genetic forms of the disease (Maron et al 1984).

These accumulated observations on the patterns
of inheritance strongly indicate the importance of
genetic counseling that should be individualized, par-
ticularly to those young children with a positive fa-
mily history of hypertrophic cardiomyopathy. If the
echocardiographic examination initially was normal
in such children, follow-up echocardiograms should
be carried out at approximately 3 year intervals until
the patient attains adult age and mature body size.
The importance of genetic counseling should be em-
phasized to families and relatives related to those who
have hypertrophic cardiomyopathy not only for scien-
tific interest but also for their safety, since the risk of
premature sudden death is associated with hyper-
trrophic cardiomyopathy, particularly among those
who participate in vigorous athletic activities (Maron
et al. 1980 & 1982). Genetic counseling in the future
should include not only echocardiographic techniques
but also new genetic technologies such as enzymat-
ic fragmentation of DNA or cell hybridization studies

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and chromosome analysis to pinpoint the precise loci of abnormal genes.

HYPERLIPIDEMIA IN ATHEROSCLEROTIC HEART DISEASE

Osler first pointed out that heart attacks run in certain families and a large body of literature now firmly documents the familial aggregation of coronary atherosclerosis. This aggregation is due largely to familial clustering of genetically determined risk factors such as hyperlipidemia, diabetes mellitus and hypertension. Of all these risk factors, elevated blood cholesterol and triglyceride appear to have a direct impact on the pathogenesis of atherosclerosis (Osler 1897; Slack and Evans 1966).

Three simply inherited forms of hyperlipidemia were identified: familial hypercholesterolemia, familial hypertriglyceridemia and familial hypercholesterolemia, familial hypertriglyceridemia and familial hyperlipidemia. Together, these three disorders were present in 20% of myocardial infarction survivors under 60 years of age. In fact, these disorders appeared to be transmitted by a single gene mechanism, indicating that each disorder may be caused by a single biochemical defect at the molecular level.

Familial hypercholesterolemia occurs in two genetically and clinically distinct forms. Heterozygotes, who inherit one mutant gene, manifest from the time of birth a 2 to 3 fold elevation in plasma cholesterol and as a adult, may develop tendinous xanthomas and premature coronary heart disease. Approximately 1 out of 20 survivors of myocardial infarction amid the general population turns out to be heterozygous for this disorder (Goldstein et al. 1973). Homozygotes, who inherit a double dose of this mutant dominant gene, are much more severely affected than the heterozygotes. The plasma cholesterol level in homozygotes can be as high as 1000 mg. In addition, a unique type of cutaneous plaque-like xanthomas develop and clinically significant coronary atherosclerosis usually becomes apparent before 20 years of age (Fredrickson 1971; Brown and Goldstein 1975).

The low density lipoprotein suppresses 3-hydroxy-3-methyl-glutaryl coenzyme A reductase. The reductase controls cholesterologenesis in human fibroblasts. High density lipoprotein, on the other hand, has no effect in suppressing reductase activity (Brown et al. 1974). It appears that low density lipoprotein is involved in the transport of cholesterol into the cell and that the failure of the homozygote to respond to low density lipoprotein might be due to a specific defect in the ability of these mutant cells to interact with lipoprotein. The experimental evidence indicated that LDL binding, degradation and LDL mediated suppression of reductase activity are all controlled by the LDL receptor site on the surface of normal cells. As the concentration of LDL in the medium is increased, the saturation kinetics for binding and degradation of suppression of reductase activity in normal cells are well controlled. In the homozygotes, however, the LDL binding is virtually absent, LDL degradation is severely reduced and reductase activity is suppressed by LDL (Fig. 2). It is therefore speculated that the primary genetic abnormality in familial hypercholesterolemia resides in a gene whose product is necessary for the production of the high affinity cell surface receptor for LDL. This defect of the LDL receptor results in deficient high affinity binding of LDL.

The genetically oriented cholesterol binding and degradation is clearly demonstrated on experimental in vitro studies. When the concentration of LDL in the medium is increased, the amount of LDL binding to normal cells raises and reaches a maximum, whereas in heterozygote, the maximal binding of LDL is reduced by 60% and is zero on homozygote. The suppression of reductase activities by LDL is also proportional to the amount of LDL bound (Brown and Goldstein 1974). Thus, the regulatory gene on the LDL receptor loci may play a devastating role on familial hyperlipidemia and ischemic heart disease.

REMARKS

Advances in the knowledge of molecular biology and cytogenetics have contributed to enhance medical genetics to a new wide horizon in an unimaginable magnitude, from theoretical foundations to diagnostic as well as therapeutic implications.

Detailed knowledge of the genetic makeup of individuals, revealed by examination of DNA, is emerging as a significant component of diagnosis for inborn errors of metabolism, development of sophisticated prenatal diagnostic techniques and elucidation of genetic factors in common disorders such as atherosclerotic heart disease, congenital anomalies of heart and diabetes, etc. Furthermore, recent technical progress in molecular biology has led to isolate, by molecular cloning, virtually any one of the 100,000 genes that constitute the human genome. The structure of such genetic elements can be deciphered in exquisite detail, the nucleotide sequence altered in a predetermined way and that gene returned to a new cellular environment to study the effect of such experimental manipulations on its function. Complex mathematical and computer facilities have been de-
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veloped to unravel the patterns of such polymorphic traits to reconstruct highly detailed genetic maps. Because science is "the art of soluble", medical genetics has embraced these new tools and put them together in a multi-dimensional scope.

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