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REINTRODUCTION TO CLASSICAL GENETICS

Laird Jackson, MD

DR. NORMA DAVIS: Thank you Dr. Billings for a very interesting presentation. Our next presenter is Dr. Laird Jackson who comes from Jefferson University Hospital in Philadelphia. He’s a Professor of Medicine, Pediatrics and Obstetrics & Gynecology. After graduating from Pomona College in California, he received his medical degree at the University of Cincinnati and, I believe, has been at Jefferson University Hospital since then. He did an internal medicine residency which was followed by a fellowship in medical oncology and since 1969, he has held the position of Director of Medical Genetics where he specializes in prenatal diagnosis and genetic disorders. He teaches a formal genetics course to medical students and then participates actively in a summer genetics course conducted at the Jackson Laboratory in Maine. He’s also doing research, tracking the significant genes in evolution of colon cancer. This morning he’s going to refresh our memories, giving us a "Reintroduction to Classical Genetics." (applause)

DR. JACKSON: Well, thank you, and I add my "good morning" to that of Dr. Billings. I’ll try just to cover what should be, but probably isn’t, quite as familiar to most of you as it might have been at one time. That is, the general information that we have about inheritance in human beings. I’ll start off by referring you to the materials which I distributed to your handbook, which will have some of the terminology and definitions which I’m sure will come up from other speakers.

I’ll begin by telling you that geneticists generally think that genetic disorders come in three sorts of packages. And all of those involve the chromosomes. All of you know, of course, there are 46 of these and they come from your two parents, so we get 23, or 1/2 of the total, and 1 member of each of the pairs from each of our parents, if everything works right. The chromosomes are more or less like a shopping bag that you use when you go to the local supermarket. They are the physical structures that are used to carry your genes around on, or in. Chromosomes themselves can be disturbed to provide one category of genetic disease, a category in which an entire chromosome or a visible portion of a chromosome is involved. Obviously, the other two categories of genetic disease also involve the chromosomes, because if they involve the genes they must involve at least a place on a chromosome. So, chromosomes are entire structures, but at any one spot on a chromosome there may be a sequence of chemical information that we call a gene. And if everything again is all right, there’s the same location on the other chromosome, one of those you got from your father and one you got from your mother, that codes for the same information related to its function. It may be slightly different and make that function not work right or not work at all, or work a little bit differently, but if it is a gene for a specific biochemical function then the same function is coded for on the same spot on both chromosomes. And we call those places "loci," or the locations of the genes. We call the different forms of the genes that might occur on the two chromosomes, or even more than two forms if we’re considering chromosomes that belong to someone else in the population, "alleles." Of course, genes or alleles are specific controllers of genetic functions that Gregor Mendel, the Czechoslovakian monk, worked with in the monastery garden over 100 years ago, and discovered or described the way that these things can be transmitted down through generations of plants and generations of individuals.

There are obviously mixtures of involvement between the individuals who have these genes and chromosomes and the environment they live in. That forms another big category of genetic disease that are so-called multifactorial diseases in which there is a significant interaction between genes, which are usually not very well defined by geneticists, and the environment, which has an impact for insurance underwriters, I’m sure. Things like hypertension and coronary artery disease and hyperlipidemias are familiar terms, and those things are acknowledged to have both genetic and environmental contributors to how they manifest themselves in human beings, forming a category of disease called multifactorial disease.

The chromosomes which contain the genes that we all talk about have been fairly well looked at under the microscope with techniques that provide bands that cytogeneticists look at. Of course, we have changes in how the people who are affected by chromosomal diseases are treated and survive in society, much the way Dr. Billings told you about cystic fibrosis patients. Down’s Syndrome, which is probably the most widely recognized chromosomal disorder, is associated with the presence of an extra chromosome 21. Not too long ago, the life expectancy of these children was much less.
than it is today. Their access to benefits such as good education was severely restricted compared to what it is today and a high percentage of these children were found in state or public institutions. This is no longer true, because we’ve changed our attitude and approach to these children. I’m sure that has changed the costs of caring for these kids and some of the costs are spread in different areas than they used to be, because they are spread out over educational as well as health benefits.

Chromosome disorders also may have a significance for consideration of health and other forms of insurance. There are actual translocations, with the net effect that there are people walking around who are perfectly normal, who are healthy, who have no downside to any kind of health insurance or life insurance, but who have a risk in reproduction of transmitting this chromosomal rearrangement, and giving birth either to a compromised child or having a high risk for reproductive failure.

Chromosomes also sometimes lead us in genetics into insights, into both single gene disorders and perhaps increasingly into what we categorize as multifactorial disorders, but disorders in which single gene effects may have a larger significance than we thought in the past.

Well, let’s take a look at some of the examples of classical single gene inherited genetic disorders of the type that Mendel foreshadowed in his plant work, and for which we call them Mendelian disorders. We characteristically divide up Mendelian disorders into those that effect genes carried on chromosomes that do not relate to your sex, and we call those chromosomes autosomes, and on the chromosomes that do relate to your sex, and the one of those that generally carries significant genes is the X chromosome, found in double dose in females and single dose in males. Further, we divide single gene disorders up into those that are manifest when a single, abnormal gene is present and we usually refer those as dominant, and those in which it takes both genes to be abnormal and we refer to those as recessive. When we’re talking about dominant and recessive genes, we’re talking not really about the genes but talking about the traits that we see in people, because when we get down to being able to measure what the gene does, we don’t need the terms dominant and recessive anymore.

Each of these will be covered in some detail but the following lists the major categories of genetic problems with which medicine is concerned:

a. Single Gene (Mendelian) Disorders

These are conditions inherited through single genes and except for new mutations, generally follow the Mendelian rules of inheritance. The major patterns of inheritance are autosomal dominant (AD), autosomal recessive (AR) and X-linked. At last count (By McKusick 07-10-91), there were the following number of defined and suspected disorders in each of these categories.

<table>
<thead>
<tr>
<th>Pattern of Inheritance</th>
<th>Defined</th>
<th>Suspected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal Dominant</td>
<td>2470</td>
<td>1241</td>
<td>3711</td>
</tr>
<tr>
<td>Autosomal Recessive</td>
<td>647</td>
<td>984</td>
<td>1631</td>
</tr>
<tr>
<td>X-Linked</td>
<td>190</td>
<td>178</td>
<td>368</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3307</strong></td>
<td><strong>2403</strong></td>
<td><strong>5710</strong></td>
</tr>
</tbody>
</table>

b. Chromosomal Disorders

These are conditions which result from abnormalities in chromosome number and/or structure. Some are inherited and heritable, but most arise as new genetic accidents which are only infrequently transmissable. They are usually associated with somatic malformations and with mental retardation or abnormalities of sexual development, or both.

c. Multifactorial Disorders

These are conditions which have or appear to have genetic components which do not follow strict Mendelian rules and which appear to be influenced by environmental (= non-genetic) factors. This group includes many common congenital malformations as well as several common disorders of adult life.

Taking a Genetic History

The medical history to be taken when a genetic disorder is suspected is not really different from a conventional medical history except, of course, that genetic and familial aspects are searched for more carefully. The record of genetic history is usually presented in the form of a pedigree. Most of the conventional symbols used in pedigrees are given below, as is a description of how a pedigree is obtained and drawn. The value of the pedigree is only as good as is the skill with which it is obtained. The correct questions must be asked, and these questions must be oriented to the problems which are under consideration. This is true for any family history which is part of a medical evaluation and not just for a history being taken for specific genetic indications.
Begin pedigree with the index patient of client (identified by an arrow), then include as a minimum the following living and dead relatives of the patient or client, in this order: siblings, parents, father's siblings, all descendants of father's siblings, father's parents, mother's siblings, all descendants of mother's sibling, mother's parents and finally all descendants of both the patient himself and his siblings. Within sibship list sibs (including miscarriages, abortions, stillbirths) in order of birth (oldest to youngest). Put ages under all symbols - oldest sibling on the left. List health status under each one.

Figure 1

- PEDIGREE SYMBOLS -

- affected male - unaffected male
- affected female - unaffected female
- proposita (may be affected or unaffected)
- bar over symbol personally examined
- propositus
- or - one person sex unknown
- five persons of unknown sex
- abortion (miscarriage) of unknown male, female sex
- dead
- identical twins
- non identical twins
- twin zygosity unknown
- minimally or unaffected "carrier" or proven transmitter
- "short hand" half sib designation
- no offspring, sterility, sterilization or reproductive period ended

I

II

III

IV

V

IV 1, 2 unmarried
SB stillborn
ID infant death
If there is another member in the household having another qualifying disorder, extend the pedigree to include the above relatives to this latter case as well (or make a separate pedigree if this is easier).

Include the parents of all persons in the oldest generation shown who have the same affliction as the index patient.

Do not include spouses of patient's relatives unless relatives offspring are affected.

Don’t forget to include stillborn relatives in the pedigree. The symbol for stillborns is smaller and not extended as far as other siblings. Include reason for stillbirth, if possible.

Include miscarriage-abortion symbol when appropriate.

Different ethnic groups have differing incidences of genetic polymorphisms such as blood groups or serum types. The same also pertains to frequencies of disease. Each ethnic group seems to have a number of disorders which are more common in that group than in others, and recognition of such differences is of great importance when diagnosis and counseling are being undertaken. Examples of such ethnic differences are the prevalence of HbS (sickle cell disease) in blacks (related to their origin from the central African plain), Tay-Sachs disease in Ashkenazic Jews (related to consanguinity of historic origin), and the varying mutations for cystic fibrosis among various European subgroups. Because of these differences, it is important to obtain information about the ethnic background of all individuals in whom a genetic problem is suspected or who have an obscure problem that could conceivably be genetic in origin.

Mendelian Disorders

Pedigree analysis may reveal a pattern of transmission of a trait or disorder throughout a family. The most common clinical patterns are termed "dominant" when the probability that a gene carrier will transmit the trait, hence produce an affected offspring, is 50%; and "recessive" when two carriers are required to produce an affected person (except with X-linked recessive inheritance). These terms refer to the traits, not the genes. When the action of the gene is understood, the terms dominant and recessive become unnecessary to describe the gene. In proper use a dominant condition is one which appears and is recognizable in the heterozygous state while a recessive condition requires a homozygous (or hemizygous in X-linkage) genetic state to become manifest. Autosomal Dominant Traits

Autosomal dominant disorders are conditions caused by genes carried on the autosomal chromosomes which produce a clinically recognizable condition when the gene is present in the heterozygous state. The trait or condition may be transmitted from one generation to the next and the probability that a gene carrier will transmit the trait is 50%. On the average, half of the offspring of an affected person will be affected. A typical pedigree is illustrated.

![Figure 2](Typical Autosomal Dominant Pedigree. Both sexes are affected, and transmission occurs through both sexes. The heterozygote is affected.)

Autosomal dominant conditions exhibit two related (and often confused) characteristics, knowledge of which is helpful in the diagnosis and counseling of patients. Penetrance is the percentage of individuals carrying a dominant gene who show recognizable signs of it. It is expressed as a percentage of a group of individuals; at the individual patient level it is an all or none phenomenon, i.e., the gene is recognizable or it isn't so the gene is penetrant or it isn't. Obviously, careful clinical observations, laboratory studies, special biochemical tests and the like, all improve our ability to recognize the effects of a gene and increase the percentage of "penetrance." This phenomenon may occur where no symptoms are ever produced even though the gene is present (for example only 95% of gene carriers of the retinoblastoma gene which causes an eye tumor, develop the tumor. The gene is 95% "penetrant"). Penetrance may also be age-dependent especially in degenerative neurological conditions of adult onset. That is, there is a span of years over which the gene may make its clinical appearance. Huntington's chorea (the disorder which affected Woody Guthrie, the folk-singer) is a classic example where many individuals don't show signs until their 50's but the average age of onset is in the 30's.
Expressivity is an expression describing clinical variation in the nature and severity of symptoms and signs present in any person with a gene disorder, especially autosomal dominant disorders. It refers to how seriously affected an individual is (therefore an individual, not a group phenomenon). Expressivity can only be discussed when a condition is "penetrant." Both expressivity and penetrance are frequently abused terms and are used to obscure imperfect understanding of the clinical presentation or the pedigree pattern of genetic conditions. Try not to fall into this trap.

A final problem occurring with dominant conditions is that many affected individuals will be the result of new mutations. As only one mutant gene is required to produce a recognizable condition, this will occur with some frequency. The more severe the condition, the more likely the case is the result of a mutation. The extreme example is where the gene is lethal (i.e., does not permit reproduction) and all cases must be the result of new mutations. In that case H, the mutation rate, equals half the disease frequency (H=1/2 disease frequency). This is because the disease frequency is expressed per number of persons (1/100,000 persons) while each person has two genes at a locus and mutation rates are expressed per gene. In counseling it is sometimes difficult to estimate the chance that an affected person is due to a new mutation and not the result of a parent in whom the gene is non-penetrant. Estimates of most mutation rates are in the range of 0.5 x 10^5 to 10^4.

Autosomal Recessive Inheritance

Recessive genetic traits, in general, are those where two alleles must be present to be expressed as a trait or where the normal allele must exist alone unchallenged by a normal or wild-type allele. Autosomal recessive traits are caused by genes carried on autosomes so that parents of affected children are, by definition, obligate heterozygotes for the gene; affected persons within families are siblings; and males and females are affected in equal numbers providing the numbers are sufficiently large. Heterozygous parents who "carry" one gene are at 50% risk with each child to produce another carrier when only one parent carries the gene. If both parents are carriers (called a "carrier-couple") then their risk is 25% that the child will be homozygous normal (GG for gene "g") 50% that the child will be a heterozygous carrier (Gg) and 25% that the child will be homozygous affected (gg). Other ways of expressing the same figures are that in an "ideal" family, the ratio will be 1 homozygous normal to 2 heterozygous carriers to 1 homozygous affected. Be careful and remember that the risks among the normal children are 1/3 that the child will be a normal homozygote and 2/3 that it will be a heterozygote.

In general, autosomal recessive traits are more likely to involve some biochemical enzymatic mechanism than are dominant traits. This may simply reflect our ignorance of the basic abnormality in most dominant traits as compared with some outstanding recessive conditions. In the future, there may be biochemical mechanisms elucidated for all genetic conditions, an assumption predicted by the DNA-RNA-Protein central dogma. For now, most of the biochemical enzymes we understand are faulty when completely or nearly completely absent of ineffective, hence the recessive behavior. A few exceptions to this have recently been described (see Goldstein, J. and Brown, M. in text references or in Prog Med Genet 1976;1:103 [new series] or Am J Med 1975;58:147.) for example in hypercholesterolemia.

In the analysis of pedigrees to prove autosomal recessive inheritance, on ens into a special problem. Parents who are heterozygous carriers but do not have any affected children will not be detected (except with current biochemical screening programs for carriers), and therefore, the children of such parents will not be counted as unaffected offspring of carrier parents. As an example, in two-children families, the chance that any child will be unaffected is 3/4; that both children will be unaffected is 3/4 X 3/4 = 9/16 or 56% chance that such a family will not be ascertained. The remaining 44% of families (7/16) will have one (6/16) or two (1/16) children affected. This leaves us finding only 7 of 16 "at risk" families with two children each and 8 (6 x 1 - 1 X 2) children of the 14 are affected for a ratio of 0.57 instead of 0.25 as we expect. This is because we missed the other 9 families. Therea re formulae for correcting for this "bias of ascertainment" where all sibships with one
or more affected children in a population have been ascertained. These may be found in Emery and Rimoin.

Another source of bias may be introduced by the manner in which the family is ascertained if total ascertainment is not achieved. In a medical school class the number of males and females in the students' sibships was "ascertained." There were 315 males and 253 females for a sex ratio of 1.25% or slightly different than the 1 that was expected. However, the 35 women students had 38 sisters and 40 brothers. The 105 male students had 170 brothers and 180 sisters so that there were 210 male sibs and 218 female sibs for a ratio of 0.96 - much closer to the truth. The correction made was the expedient one of removing the class members themselves - the propositi. This is called the simple sib method and is useful where families with more than a single affected individual are more likely to be ascertained than families with one affected - as for example in a literature search for a rare condition.

Risk Prediction in Recessive Disorders

When accurate identification of carriers of recessive genes is not possible (as it is not in most cases) when risk prediction must depend on the use of statistical probabilities. For marriages at random within the population this means using the known frequency of the disease and calculating other needed numbers. When marriages occur among close relatives (consanguinity) then slightly different calculations apply.

The frequency of recessive diseases within populations can be estimated from existing cases (disease prevalence) or surveyed in new births (disease incidence) through newborn screening programs of various kinds. In either case, one arrives at what is usually a small number of one in several thousand chances or births. An example is the frequency of albinism which is said to be about 1 in 10,000 or .0001: There is a formula for calculating the occurrence of carriers of this gene in the population when the incidence is known and it is derived from the famous Hardy-Weinberg equilibrium (see later). This "law" shows that two alternative forms of a gene (alleles) called p for the dominant form and q for the recessive will occur at population frequencies which add up to unit (p+q=1). Expansion of this so that we can describe the equilibrium of homozygous normal - p^2 (since the probability that p will exist at the two homologous loci which each individual has is p x p = p^2), heterozygotes - 2pq and homozygous affected - q^2 which of course is the disease incidence or frequency and in his case is .0001 x 1 x 2 or .01 x 2 = .02 or 1/50. The utility of this number is that one can answer questions regarding the risk of marriage between carriers.

Within the random population this is obviously 1/50 x 1/50 = 1/2500 (.004). If we are speaking to a sibling of an albino then the sib's chance of being a carrier is .67 (work it out on a pedigree) and the chance of a marriage between carriers in .67 x .02 = .0133 or 1/75. The risk that they will have an affected child is 1/4 so the risk that a sib of an albino will have an albino child in any pregnancy with a random mate is 1/300 or .0033.

The situation is changed if the sib marries a relative. Depending on the degree of relationship, the risk is elevated significantly or modestly. Generally, marriages between first cousins or closer are prohibited by law or convention. First cousins carry 1/8 of their genes in common (easily computed as each direct relation has 1/2 genes in common, i.e., sibs, parent-child). Simply multiply the 1/2 probabilities in sequence. Uncle-niece share 1/4 (as do aunt-nephew, etc.), first-cousins once-removed 1/16 and second cousins 1/32. Since our albino's sib marries a first cousin this raises the risk of a carrier mating to 2/3 x 1/8 = 1/12 or .0833 and the risk of an affected child to 1/48 or .0208. This is more than 6 times the risk in a random mating.

X-Linked Inheritance

Males and females possess different sex chromosomes, and therefore must have some mechanism for handling the inheritance of mutant (or normal) genes carried on the sex chromosomes. For practical purposes the Y chromosome which is extremely small and has a large block of inactive heterochromatin, has only genes which direct sex determination and testicular development (see above). Therefore, the male has no complimentary set of genes for those carried on the X gene on the X (usually a recessive) will express it fully and are called hemizygous. Female carriers are heterozygous and are protected from expression by a mechanism different from that which operates with autosomal recessive genes (see below).

Figure 4

X-linked recessive pedigree showing, as expected, only affected males. Remember that in X-linked disorders where condition is not severe enough to preclude survival and reproduction, all daughters of affected males will be carriers. None of his sons, however, will be affected.
Pedigree transmission of X-linked traits follows the distribution of the X chromosomes and typical X-linked pedigrees as shown below. The X-linked recessive (XLR) trait is by far the most common of the two. Unaffected carriers of XLR traits will transmit the gene to 1/2 of their sons who will be hemizygous and express the trait. The carriers will also transmit the gene to 1/2 of their daughters who will be heterozygous unaffected carriers like themselves. The hemizygous male will transmit the gene to all of his daughters, making them carriers. He cannot transmit an X-linked gene to his sons as he does not transmit an X chromosome to his sons.

Carrier females have a 50% chance of any son being affected; a 50% chance of any daughter being a carrier. Affected males have all carrier daughters; no affected sons.

Occasionally a condition prevents the male from reproducing in which case it is difficult to distinguish XL inheritance from sex-limited autosomal dominant (dominant but expressed only in the male) unless linkage or other studies can clarify the question.

Dosage compensation for X-linked genes equalizes the effect of these genes in the two sexes by making only one X in each cell active in expressing its genes via gene products. This means that the second normal X (or any extra X) is inactivated by a mechanism described by Mary Lyon in the 1960's. This is often referred to as the Lyon hypothesis or as "Lyonization" of the extra X(s). The inactivation process: a) occurs early in embryogenesis at about the 10th day, b) is random so usually 1/2 of the cells present on the day of decision have the paternal X active and 1/2 the maternal X. Obviously there are rare marked deviations from this average. c) is permanent or irreversible so that the daughter cells of any cell after inactivation will follow the pattern of the parent cell. d) results in any inactivated X condensing down to form a heteropyknotic mass at the periphery of the nuclear membrane (as a Barr body).

This mechanism also has implications for the female heterozygote with an abnormal X-linked gene. Since inactivation is random and daughter cells follow the lead of the parent, the heterozygous female has a mosaic population of cells with regard to X-linked genes consisting of cells carrying the mutant allele active. The latter would be functionally like the cells of an affected male. This can be demonstrated with several systems, the classic being that of the red cell enzyme, glucose-6-phosphate-dehydrogenase (G-6PD). The enzyme is one which is found in an X-linked deficient state in black males, making them sensitive to antimalarias (and other drugs) which cause hemolysis and anemia. The female carrier can be shown to have two populations of cells by direct cell staining for G-6PD activity - normal and deficient. The mixture of cells varies, but hovers near the 50/50 range. Some conditions lead to geographic mosaicism in the carrier. Certain X-linked eye disorders involving the retina may produce a visible mosaicism on examination of the retina. X-linked genes responsible for enzyme activity may be analyzed by assay of the enzyme from hair roots which will demonstrate mosaicism in the heterozygous female as each hair root is effectively a "clone" originating from a single cell. Occasionally the distribution of inactivated cells may be skewed so as to make it nearly impossible to detect a carrier due to the small number of cells with the mutant gene, or to conversely make a heterozygous female manifest the disorder due to the preponderance of cells with the mutant gene's X active.

Carrier tests for X-linked conditions have improved in the past few years. A special concern exists in counseling for these conditions as a carrier is solely responsible for transmission of the mutant gene - the male donating no counterbalancing gene in the case of an affected son. Therefore, the genetic status of the male mate is of no concern. When a new or single case of known X-linked disease occurs in a family it is of concern to differentiate between a spontaneous mutant origin or simply a long dormant gene which has not previously been manifest in an affected male. The risk that any unknown case is due to a transmitted gene from a carrier mother would be at least 2/3 from calculations based on the mutation rate and other observations. The safest thing to do is assume the mother of a single case is a carrier and proceed from there. Mothers with 2 affected sons, one affected son and an affected male relative, or an affected father can be assumed to be carriers.
Osteogenesis imperfecta is a genetic syndrome that illustrates the pleiotropic effects of dominant genes, illustrates the clinical variability of dominant genes and is one that has been worked on by DNA researcher at my institution, Darwin Prockop, who demonstrated that this syndrome was not due to a bone gene, but to a component of bone, collagen. And he showed that mutations in collagen are what, in fact, lead to osteogenesis imperfecta. Darwin went on from there to look at other more common, but less certainly genetic conditions. Darwin has extended this to show that about 5% of all persons with aortic aneurysms have detectable mutations in collagen genes; 10% of all people with progressive osteoarthritis have detectable mutations in a collagen gene; and, for those people with other bone disorders or other common disorders affecting structural parts of the skeletal system, there are probably equally discoverable mutations, which, in the future, may change our attitude towards some of these disorders, just as our attitudes are being changed by the discoveries of genes in cancers.

DR. DAVIS: If there are one or two questions perhaps, we can entertain them.

DR. ROBERT POKORSKI, North American Reassurance Company: Excuse me, just one quick question. Actually it’s not a quick question, and I hesitate to ask it, but I will ask it anyhow. I was reading your CV and I see that you’re an expert in colon cancer genes. We read so much about this and you can’t pick up Science magazine anymore except you’ll read an article about this. Could you tell us briefly, if you can, what is the state-of-the-art? How many people are affected with this gene? Is there going to be a screening program in the future? Is there a thought that if we detect people with abnormal genes, we can screen them so that they don’t develop cancer in the future? Where are we headed with this?

DR. JACKSON: You’re right, it’s not a short question, and I’m far from an expert on colon cancer diseases. I’m not sure that you would find the total expert in any one body these days, because it’s a paradigm for where we sit. I think it is at least as good a paradigm as the breast cancer issue these days, and probably better at its present state. The gene for familial polyposis, which is also the same gene for what’s called Gardner’s syndrome, although affected in a different place (Gardner’s syndrome differs from familial polyposis in that there are extra colonic manifestations of the gene in the bone, etc.), doesn’t affect a very significant proportion of the population, or a very significant proportion of the people who have colon cancer, although that gene is ultimately affected in their colon cancers. It is not the first change or it is not inherited within the family so that they are predisposed from birth for colon cancer. But it is probably part of a progression of gene alterations which, over a protracted period of time, lead to the manifestation of colon cancer. There are genes that are both specific to the colon such as the polyposis gene, the DCC and the MCC genes, and there are genes which are general to cancer, such as the P53 gene, which appears to be a cellular gene, that are involved here. One could obviously test within polyposis families for the predisposition to colon cancer, and that would allow you to do two important things. One, to institute the kind of colonoscopic surveillance for those people who have the gene, and, two, probably equally importantly, to let off the hook those people who don’t have the gene. If applied properly, this would have the beneficial effect of constricting those with the gene to be compliant to what is not necessarily a very fun procedure. And this would, in the long run, obviously benefit them.

How to use this information for the general population is much more problematic. But there are obviously pieces of progress is being made. For example, Vogelstein’s group has shown that in simple stool specimens, you can screen for the ras mutation. Obviously that’s coming from already changed colonic epithelial cells, but this suggests that you will find ways to find even earlier changes in polypoid cells, in the colon or even just changes in their appearance without an anatomical change, that will help you to foreshadow people who may develop this lesion.

The techniques are available. How to pick up the few cells that signal a change towards malignant progression early enough, or perhaps even more importantly, how to segregate primary changes from those that promote metastasis, are things that I don’t think are answered yet. But, clearly, DNA tools begin to offer us techniques that will do that in contrast to the poor attempts that have been made in the past. Thank you.

(applause)

DR. DAVIS: Thank you Dr. Jackson.