The Genes for Color Vision

Recently isolated, the genes encoding the color-detecting proteins of the human eye have yielded new clues about the evolution of normal color vision and the genetic bases of color blindness

by Jeremy Nathans

"Colors," said Leigh Hunt, a 19th-century poet, "are the smiles of Nature." Just how does an observer distinguish one smile from another? To a great extent the answer lies in the three classes of cone-shaped, color-sensing cells in the retina of the eye. Each class responds differently to light reflected from a colored object, depending on whether the cells have within them red, green or blue pigments: light-absorbing proteins particularly sensitive to wavelengths in either the long-wave (red), intermediate-wave (green) or short-wave (blue) region of the visible spectrum. The relative amounts of light absorbed by each class of cones are translated into electrical signals by retinal nerves and then transmitted to the brain, where the overall pattern evokes the sensation of a specific hue.

The role of the pigments in color discrimination has been known for decades, and yet their structures were not elucidated until recently. My colleagues and I have now identified the genes that code for the pigments, deciphered their structures and thereby deduced the amino acid sequences of the encoded proteins. This work, completed at the Stanford University School of Medicine, should soon lead to the isolation of the pigments themselves and a detailed examination of how they function. Our studies have also provided clues to the evolution of normal color perception and the variant color vision that is often called color blindness. (Actually the term is a misnomer: few people perceive no color at all.)

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The new findings add detail to a picture of color vision pieced together over the past several centuries. Isaac Newton made the first major contribution some 300 years ago when he discovered the color spectrum. He found that sunlight, or white light, decomposes into a continuous sequence of colors when it is refracted by a glass prism. He also recognized that light at each angle of refraction has a characteristic color, ranging from red for the least-refracted rays through orange, yellow, green, blue and violet for rays that are refracted progressively more. Today each angle of refraction, and hence each pure color, is known to correspond to light of a distinct wavelength.

Newton further observed that the human eye often cannot distinguish between colors formed by quite different combinations of lights. He found, for example, that certain pairs of lights with different angles of refraction, such as red and green, could be mixed to produce a color sensation indistinguishable from the sensation produced by a pure third light—yellow in this case—whose angle of refraction was intermediate between those of the original lights.

By the late 18th century workers had extended Newton's observations and learned that color vision is trichromatic. This means most colors can be matched by a mixture of three primary lights; in all other instances a match can be achieved by mixing two of the primaries as before but adding the third primary to the given color. A variety of monochromatic, or pure, lights can act as primaries, but all sets of primaries consist of one long-wave, one intermediate-wave and one short-wave light; when the three primaries are mixed in equal parts, they produce the sensation of white. By convention, red, green and blue lights are today considered to be "the" primaries.

The English physician and physicist Thomas Young suggested in 1802 that trichromacy is a reflection of human physiology. He proposed that the colors one sees are determined by the relative extents of excitation of three types of sensors. "As it is almost impossible to conceive each sensitive point of the retina to contain an infinite number of particles, each capable of vibrating in perfect unison with every possible undulation," he noted, "it becomes necessary to suppose the number limited, for instance, to the three primary colors." It took time, but Young was eventually shown to be correct. The three classes of sensors—the cones—are now known to have overlapping but distinct sensitivities to light. For instance, the red and green receptors both absorb orange light, but the red receptor does so more efficiently.

Shortly before Young put forward his theory, a contemporary, John Dalton (the father of atomic theory), helped to arouse interest in the study of variant color vision. Such work has paralleled and greatly informed the study of normal color vision. In Dalton's first paper to the Manchester Literary and Philosophical Society, published in 1794, he reported that he did not see colors as others saw them. "That part of the image which others call red appears to me little more than a shade or defect of light," he said. He also added that orange, yellow and green appeared to him as "what I should call different shades of yellow." Today deficiencies in the ability to discriminate between colors in the red-to-green region of the spectrum ("red-green discrimination"), which are found in roughly 8 percent of Caucasian males and 1 percent of females, are sometimes referred to as Daltonism. Defects in the ability to distinguish among colors in the blue part of the spectrum also

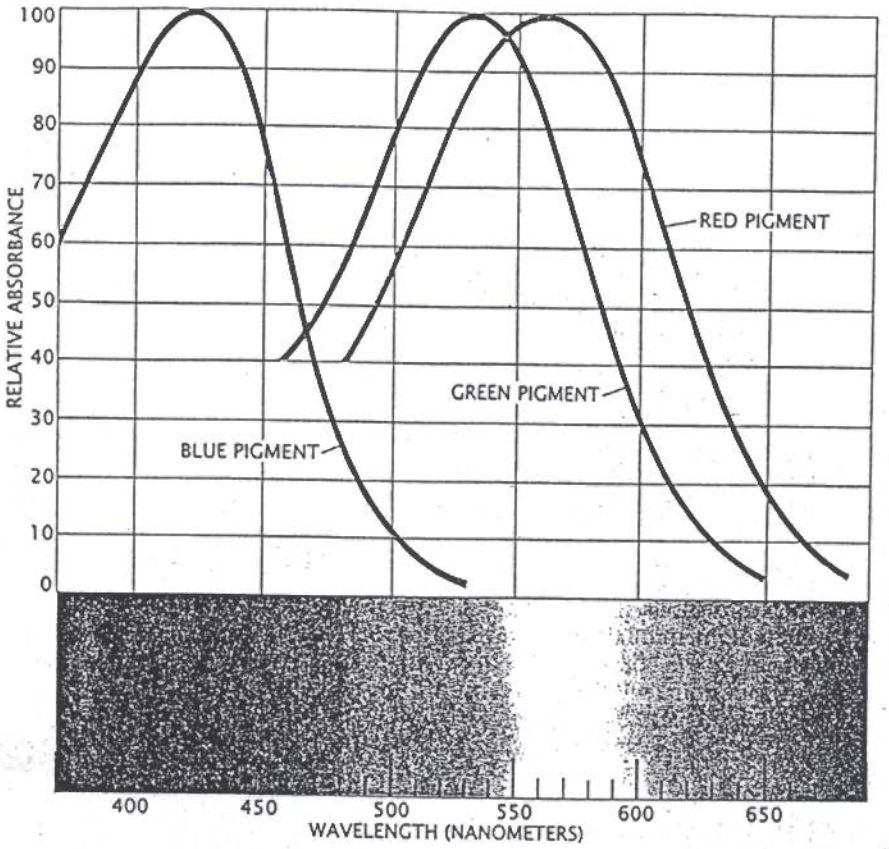
occur but are rare; I shall not discuss them in detail.

In the mid-19th century the Scottish physicist James Clerk Maxwell identified two types of Daltonism by displaying various colors to his subjects and then systematically examining the colors they could not distinguish [see "Visual Pigments and Color Blindness," by W. A. H. Rushton; SCIENTIFIC AMERICAN, March, 1975]. Following Young's three-receptor theory, Maxwell estimated the light sensitivities of the three receptors and divided his color-variant subjects according to whether they confused colors that equally excited either the red and blue or the green and blue receptors; presumably subjects with normal color vision distinguished such colors by differences in the excitation levels of their green and red receptors respectively. Maxwell correctly inferred that one group of color-variant subjects was missing the green receptor and the other group was missing the red. I and others refer to these groups as green$^-$ (green-minus) or red$^-$ (red-minus) dichromats.

Later in the 19th century the English mathematician and physicist John William Strutt, better known as Lord Rayleigh, introduced the anomaloscope, a device that even to this day is the centerpiece of color-vision testing. The anomaloscope projects three different monochromatic lights onto a screen. In studies of color discrimination in the red-to-green part of the spectrum a deep red and a green light are projected onto half of the screen so that they mix, and a yellow light is projected separately onto the other half; subjects adjust the ratio of the red light to the green as well as the intensity of the yellow light until the two halves of the screen appear to be matched.

The design of the anomaloscope relies on the fact that people with normal color vision have two classes of color detectors—the red and the green—operating at the red-to-green end of the color spectrum. (The blue sensors are not affected by the test lights.) Subjects with normal color vision perceive a match when the red and the green sensors each absorb an equal amount of light (now quantified as an equal number of photons per second) from both sides of the screen. They match the yellow with a highly reproducible ratio of red light to green light [*see illustration on page 45*]. In contrast, red$^-$ and green$^-$ dichromats can match the yellow light with either the red or the green light alone; they can also match any ratio of red and green with the yellow light. They can make such matches because all three

RAINBOW emerges when sunlight passing through droplets of water is refracted so that it divides into its constituent colors. Isaac Newton's analysis of this and a similar phenomenon—the splitting of sunlight into a spectrum of color when it passes through a glass prism—led to centuries of research into color vision. It is now known that the color one sees depends on the relative activation of three classes of visual pigments, or light-absorbing proteins, in the retina. The cone-shaped cells housing the pigments translate the absorbed light into electrical signals and transmit them to the brain for interpretation.



SPECTRAL-SENSITIVITY CURVES show the sensitivity of the three color pigments to the visible spectrum of light. The curves were plotted on the basis of data obtained by James K. Bowmaker of the Universisty of London and H. J. A. Dartnall of the University of Sussex. What is called the blue pigment is particularly responsive to the short-wavelength region of the spectrum; the green and red pigments are more sensitive to intermediate and long wavelengths. The pigments themselves have still not been isolated; hence Bowmaker and Dartnall determined their sensitivities by measuring the light absorbed by individual cones that were obtained from cadavers.

lights are detected by a single class of receptors; by adjusting the intensity of a single light, a dichromat can always equalize the number of photons captured from the two sides of the screen.

Such differences between normal subjects and red- and green- dichromats enabled Rayleigh to readily pick out the dichromats with his new device. He also identified two additional groups of color-variant subjects by testing his friends and relatives. Like normal subjects (and unlike the dichromats), these variant individuals required some mixture of red and green lights to match the yellow, but they chose unusual ratios. One group required more green and less red; the other group required the reverse. Rayleigh concluded that these subjects, now known as green-anomalous and red-anomalous trichromats, had green or red receptors with atypical spectral sensitivities.

By the mid-20th century such psychophysical studies, which depended on the judgment of subjects, strongly supported Young's three-receptor theory, and other studies had suggested that the cone cells of the retina served as those receptors. Finding direct proof for these ideas remained technically challenging, however. One major obstacle was that the cones were difficult to isolate. They are intermingled throughout the retina with the much more numerous rod cells, photoreceptors responsible for black-and-white vision in dim light.

Nevertheless, ingenuity won out. In the 1960's Paul K. Brown and George Wald of Harvard University and Edward F. MacNichol, Jr., William H. Dobelle and William B. Marks of Johns Hopkins University built microspectrophotometers capable of determining the absorbance of a single photoreceptor cell. The device passes a variable-wavelength light (one whose wavelength is changeable) through the color-detecting region of a cone and passes an identical beam through a different region, testing wavelengths across the spectrum; the difference in the intensity of the emerging beams at a specific wavelength is a measure of the absorbance of the color-detecting region at that wavelength. The studies employing the device demonstrated that cones taken at autopsy from human retinas did indeed exhibit three distinct absorbance spectra. The observed spectra agreed well with the sensitivities predicted by psychophysical studies.

A plot of the relative fraction of photons absorbed per second by each class of cones against the wavelengths of the visible spectrum yields three bell-shaped curves. The blue cones absorb wavelengths ranging from 370 nanometers (billionths of a meter) to 530 nanometers and are most sensitive to wavelengths of 420 nanometers. Both the green and the red cones are active across most of the spectrum but are particularly sensitive to wavelengths between about 450 and 620 nanometers. The green cones are most efficient at 535 nanometers, the red cones at 565 nanometers.

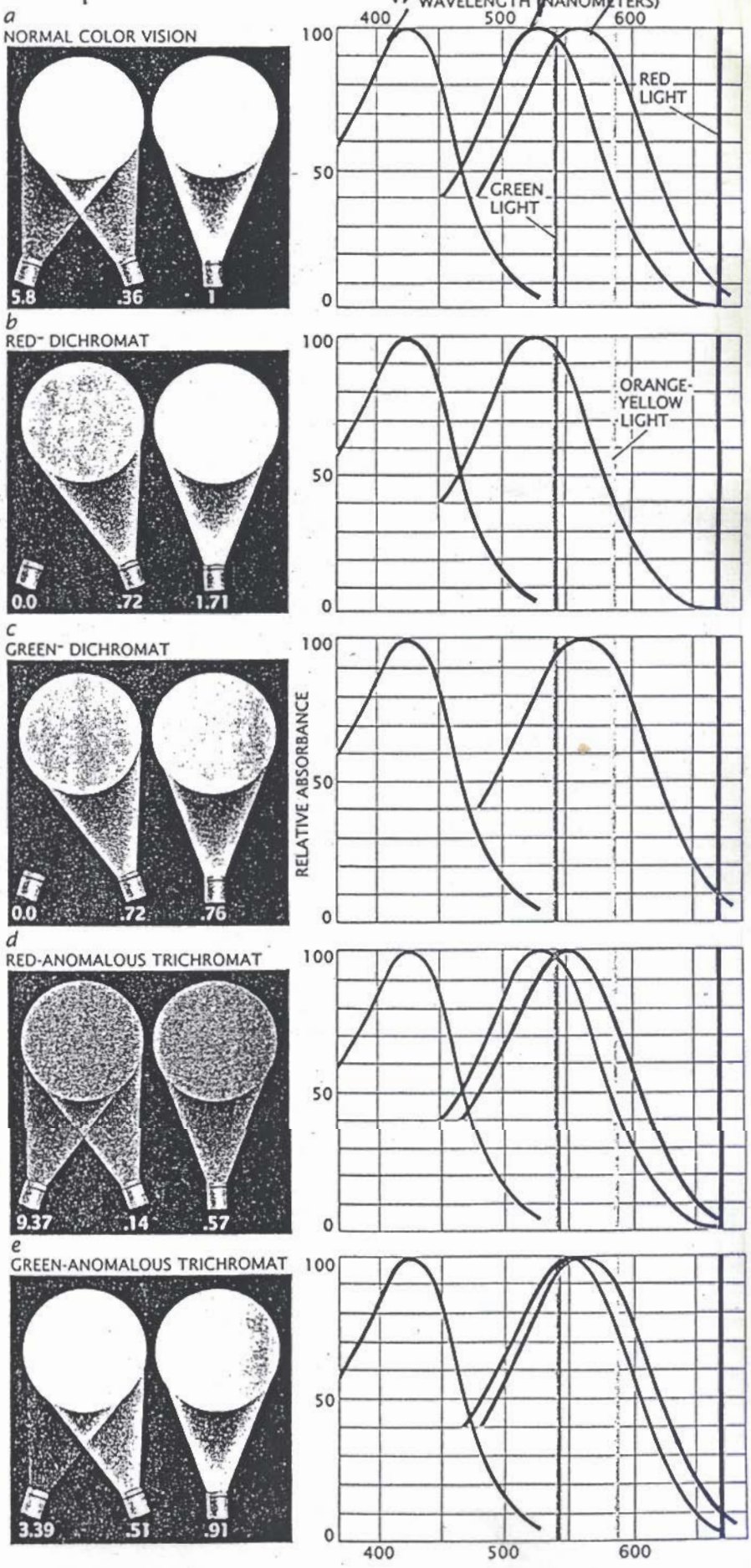
Beginning in the 1970's new evidence that dichromats lack one or another class of receptors emerged. William A. H. Rushton of the University of Cambridge directed a variable-wavelength light into the eyes of dichromats and measured the light reflected from—and hence not absorbed by—the retina; he thereby demonstrated that specific wavelengths are not absorbed normally by dichromats. More recently, James K. Bowmaker of the University of London, John D. Mollon of Cambridge and H. J. A. Dartnall of the University of Sussex showed with a microspectrophotometer that a retina obtained from a green- dichromat did not have the green class of cones.

New evidence also yielded clues to the basis of anomalous trichromacy. By means of psychophysical techniques Rushton and, separately, Thomas P. Piantanida and Harry G. Sperling, who were then at the University of Texas, demonstrated that the spectral-sensitivity curves of anomalous red and green receptors lie in the interval between the normal red and green absorbance curves.

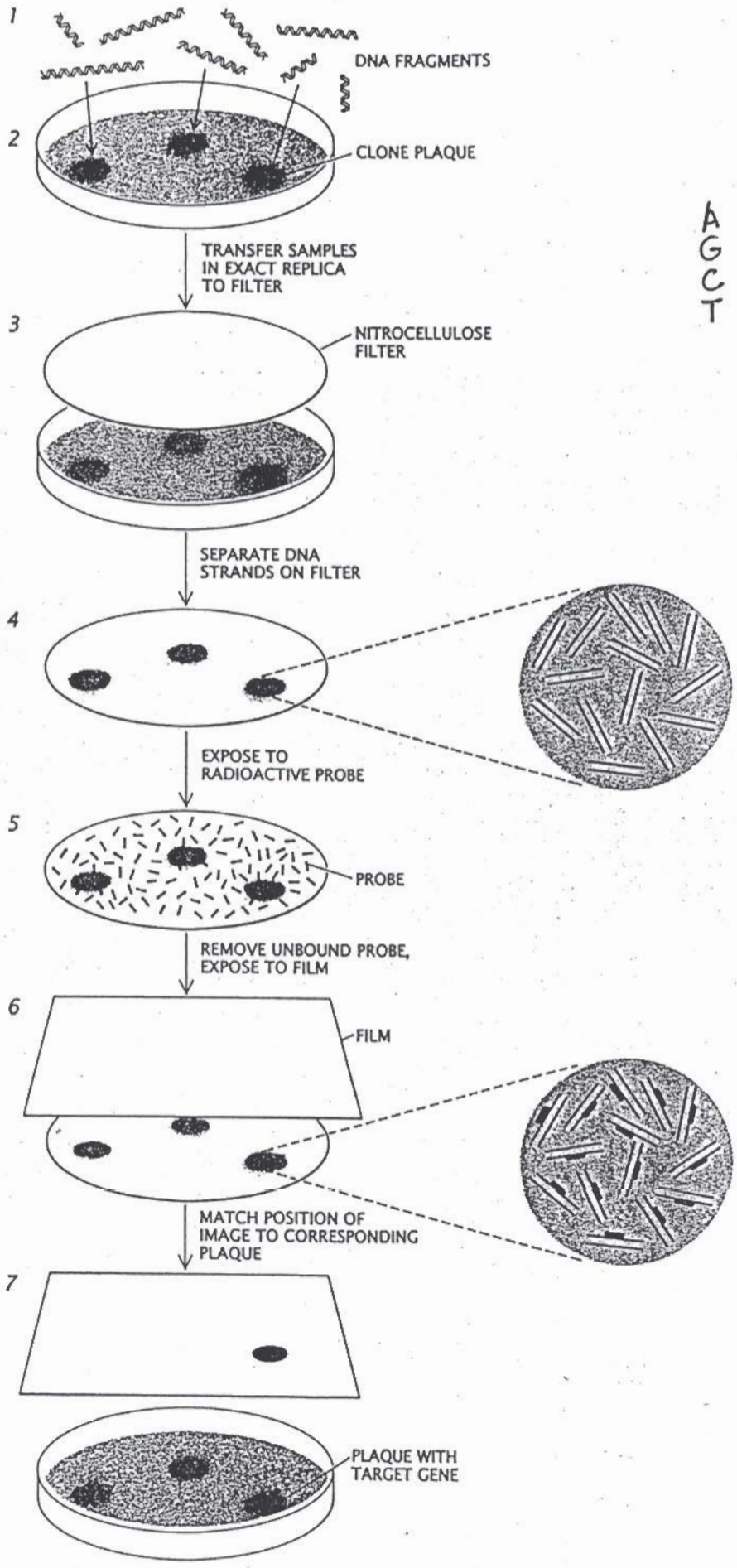
With the existence of three distinct classes of cones firmly established, in the early 1980's my colleague David S. Hogness and I turned our attention to the genetic bases of normal and abnormal color vision. In addition to aiding in the effort to isolate the pigment proteins, we hoped to supplement the findings of classical genetic studies that traced the inheritance of aberrant color vision within families.

Such studies built on the old observation that deficiencies in red-green discrimination are commoner in males than in females. Analysis of this pattern indicated that genes on the X (sex) chromosome are responsible for the variation. Males will have variant red-green discrimination if their single X chromosome (inherited from the mother) carries the trait; females will be affected only if they receive a variant X chromosome from both parents. The studies also indicated that variations in blue sensitivity are rooted in a gene on some nonsex chromosome. We planned to test the most straightforward explanation for these inheritance patterns, namely that color-vision variations result from inherited alterations in the genes encoding the cone pigments. Presumably mutations in such genes could result in the loss of a functional pigment or in the production of a pigment with an abnormal absorbance spectrum.

Our approach involved isolating the genes that code for the color pigments and comparing their structures in people with normal and variant color vision. Frequently one isolates genes by determining the amino acid sequences of the proteins they encode and parlaying that information into clues about the structure



COLOR MATCHES (*left*) made in a test of red-green color discrimination are depicted next to the subjects' spectral-sensitivity curves (*right*). The testing device, a Rayleigh anomaloscope, superposes a red and a green light on one half of a white screen and projects an orange-yellow light onto the other half. Subjects adjust the ratio of red light to green and the intensity of the yellow light until the two sides of the screen appear to match—that is, until the light absorbed by each type of pigment from one side of the screen is equal to the amount absorbed from the other side. The numbers below the lights show the relative intensities. Normal subjects (*a*) require both the red and the green light to match the yellow, choosing a high intensity of red and a low intensity of green. (The red and green pigments both absorb the red light less efficiently and the green light more efficiently than they do the yellow.) People who lack the red (*b*) or the green (*c*) pigment are identified by their ability to match the yellow light with the red or the green alone. (Only the green matches are shown.) Subjects whose red (*d*) or green (*e*) pigments have abnormal spectral sensitivities require both red light and green light to match the yellow but, compared with normal subjects, choose an excess of red or green respectively.



of the genes. Because virtually nothing was known about the structure of the color-pigment proteins when we began our work, we settled on a less direct strategy.

We started with the assumption that the cone pigments and the rod pigment, rhodopsin, all evolved from a common ancestral visual pigment and that as a result the present-day genes probably have some similar sequences of nucleotide bases: the four different chemical units whose sequence along the DNA helix encodes information. If we knew the structure of the rhodopsin gene, we reasoned, we could learn something about the structure of the cone-pigment genes. At the time neither human rhodopsin nor its gene had been isolated, but investigators had successfully isolated bovine rhodopsin from the retinas of cattle. Even better, Yuri A. Ovchinnikov and his colleagues at the M. M. Shemyakin Institute of Bioorganic Chemistry in Moscow and Paul A. Hargrave and his co-workers at Southern Illinois University had deciphered the amino acid sequence of the protein. That information would be our springboard for identifying the cone-pigment genes.

We planned to isolate the bovine rhodopsin gene and then use it as a probe to identify the human rhodopsin gene and the cone-pigment genes. The plan relied on a technique known as DNA hybridization which exploits the fact that a single strand of DNA

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DNA HYBRIDIZATION enabled the author and his colleagues to identify the genes for human rhodopsin—the pigment responsible for (colorless) vision in dim light—and its close relatives, the cone pigments. They chemically cut double-strand DNA (*1*), separated the fragments by size and cloned them in bacterial viruses grown on a lawn of bacteria. Each virus multiplied to form a plaque, a zone of viral multiplication (*2*). Nitrocellulose filter paper was placed over the dishes so that a sample from every plaque adhered (*3*). The DNA on the filter was chemically separated into single strands (*4*) and exposed to a radioactively labeled probe (*red*): a single-strand DNA from the bovine rhodopsin gene (*5*). If the probe was structurally similar to the genes for the human pigments, as it was expected to be, it would hybridize with (bind to) the pigment genes. To determine whether the probe did in fact bind, the filters were covered with photographic film (*6*). Dark spots appeared at binding sites (*7*), indicating the radioactive probe had bound. The workers then identified the clones containing the pigment genes by aligning the spots on the film with the corresponding plaques.

will form a stable double helix with a second strand if the sequence of nucleotide bases along one strand is complementary to the sequence along the other strand. In particular, the base adenine always pairs with thymine, and guanine always pairs with cytosine.

The hybridization technique has many steps, but in essence an investigator chemically cuts up the double strand of DNA to be probed and produces multiple copies of each fragment by cloning it. A sample from each clone is split into single-strand DNA, and a radioactively labeled probe, another piece of single-strand DNA, thought to be complementary to the gene one hopes to identify is added to the samples. If all goes well, the probe binds stably to its complement, thereby picking out the target gene [*see illustration on opposite page*].

Normally we would set about developing a probe that would accomplish our first aim—identifying the bovine rhodopsin gene—by generating a list of all possible base sequences that could give rise to the known amino acid sequence of rhodopsin. Then we would test a variety of probes constructed on the basis of that list. Fortunately we were spared much of the time-consuming process, because a probe for identifying the bovine rhodopsin gene was at hand. H. Gobind Khorana, Daniel D. Oprian and Arnold C. Satterthwait of the Massachusetts Institute of Technology and Meredithe L. Applebury and Wolfgang Baehr of Purdue University had already identified a DNA sequence that bound efficiently to messenger-RNA molecules encoding bovine rhodopsin. (Messenger RNA is the single-strand molecule that carries information from DNA in the nucleus to the cytoplasm, where it directs production of the encoded protein. RNA is virtually identical with the coding strand of the DNA from which it is transcribed.) Based on the DNA sequence of Khorana and Applebury and their colleagues, we synthesized a probe and used it to identify the bovine rhodopsin gene.

In the second stage of our plan we enlisted a strand of the newly identified bovine rhodopsin gene as a hybridization probe to search for the human rhodopsin and color-pigment genes. The probe bound strongly to only one segment of human DNA, which subsequent tests identified as the gene encoding human rhodopsin. Our probe also bound, although not as strongly, to three other DNA segments. When we determined their nucleotide sequences, we found the segments had coding regions that were homologous to those of the human and bovine rhodopsin genes. Analyses of the amino acid sequences of the encoded proteins showed that the molecules were also similar to one another: some 40 percent of each protein chain was identical with the sequence of rhodopsin.

We naturally suspected that the DNA segments bound by our probe were the three cone-pigment genes, but we wanted further evidence. For instance, we hoped that messenger RNA corresponding to the probe-bound sequences would be found in the retina of the eye, the only place where visual pigments, and hence visual-pigment RNA's, are produced. Sure enough, the retina did yield RNA corresponding to the probe-bound DNA.

To evaluate whether our findings were consistent with those of classical genetic studies, which would provide more evidence that we had found the color-pigment genes, we determined where on the chromosomes the DNA segments pinpointed by our probe lie. In collaboration with Thomas B. Shows and Roger L. Eddy of the Rosewell Park Memorial Institute in Buffalo, N.Y., we found that two of the three weakly hybridizing genes reside in exactly the region of the X chromosome where classical analyses had placed the source of variant red-green discrimination. We therefore concluded that these genes encode the red and green pigments, and later studies we did with Piantanida confirmed this belief. The third gene, now known to encode the blue pigment, came from chromosome 7, a finding that is consistent with the notion that variant blue color vision is determined by a nonsex chromosome.

The significant homology between the rhodopsin gene and the three cone-pigment genes suggested that all four genes had indeed evolved from the same ancestor. The available evidence supported the notion that at some early stage a primordial gene had given rise to three others: the rhodopsin gene, the blue-pigment gene and a third gene that encoded a pigment sensitive to light in the red-to-green part of the visible spectrum. This third gene recently duplicated, yielding a red- and a green-pigment gene.

We think the red- and green-pigment genes are the product of fairly recent duplication, because they have a strikingly high degree of homology: a full 98 percent of their DNA is identical, suggesting it has had little time to change. The idea that the event took place not long ago, at least in evolutionary terms, is supported by the findings of Gerald H. Jacobs of the University of California at Santa Barbara, who worked with Bowmaker and Mollon. They have shown that New World (South American) monkeys have only a single visual-pigment gene on the X chromosome. In contrast, Old World (African) monkeys, which are more closely related to human beings, appear to have two visual-pigment genes on that chromosome. The addition of the second X-chromosome gene must have occurred sometime after the separation of South America and Africa, and hence of the gene pools of the New and Old World monkeys, some 40 million years ago.

The discoveries described so far were not entirely unexpected, but another finding was. When we studied the visual-pigment genes from the X chromosome of 17 of our male colleagues, all of whom had normal color vision, we found that the red-pigment gene was always present in a single copy, but the other gene—the one encoding the green pigment—was present in one, two or three copies. The existence of multiple copies was surprising, because one green-pigment gene is presumably sufficient for normal color vision.

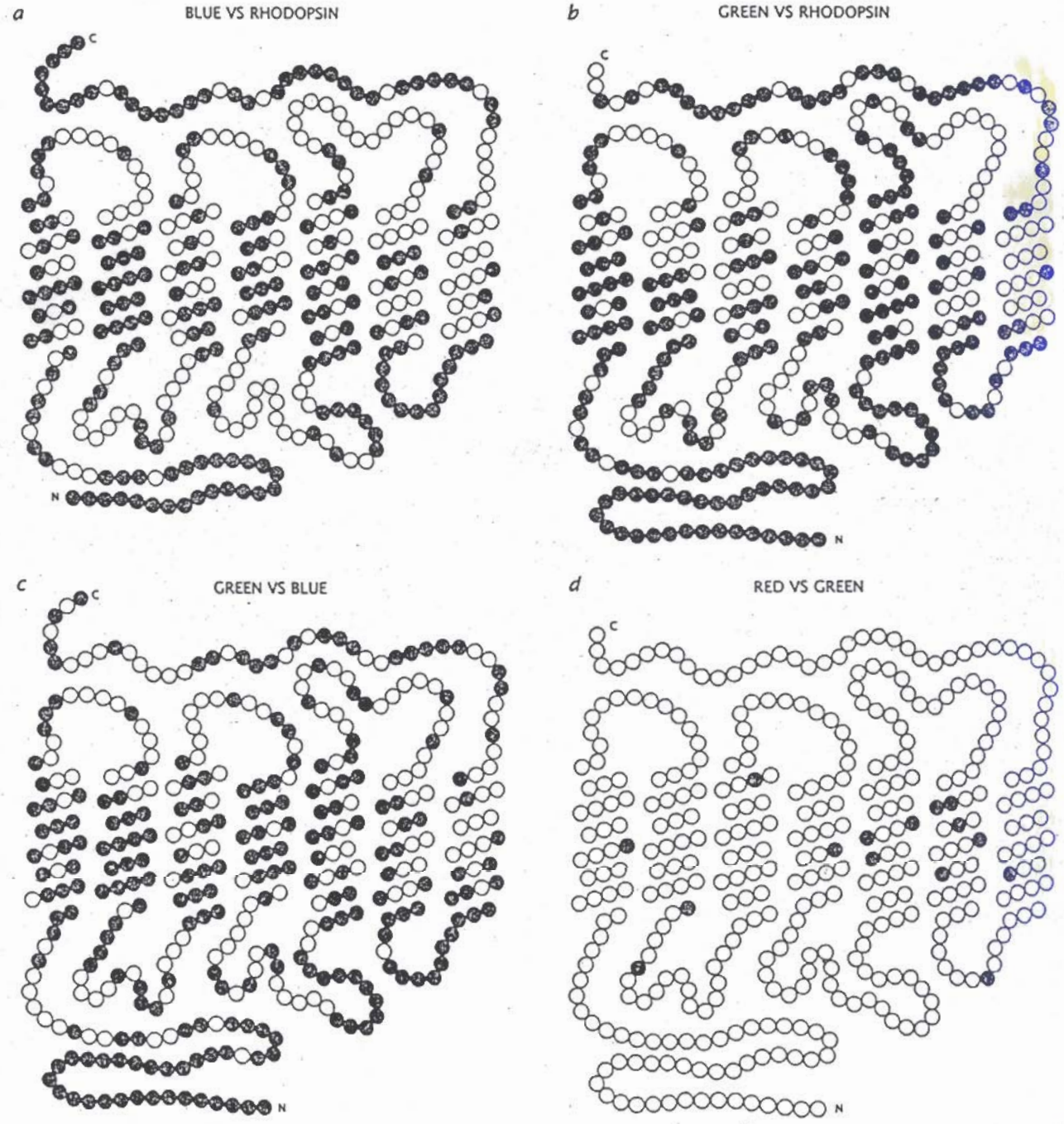
Recent experiments suggest that the visual-pigment genes lie in a head-to-tail array on the X chromosome and that the tandem arrangement accounts for the variability in gene number. Tandem genes that are similar have a tendency to undergo changes in copy number in the course of meiosis, the process of cell division that gives rise to sperm and eggs. Cells carry somewhat different versions of each chromosome; during meiosis the matching chromosomes pair up and recombine, or swap segments. Ordinarily the exchange is equal, so that each chromosome neither gains nor loses genes. Occasionally, however, two segments that are highly homologous can recombine erroneously, undergoing what is called unequal homologous recombination. Either one chromosome gains one or more copies of an existing gene at the expense of the other chromosome or the two chromosomes swap material from related but different genes. The chromosomes that result are then passed on in sperm or eggs.

It is quite easy to imagine how unequal homologous recombination might have given rise to the varied configuration of green-pigment genes

in people with normal color vision. Consider two matching chromosomes, each carrying one red-pigment gene next to two green-pigment genes. If a green-pigment gene on one of the chromosomes crossed over to the other chromosome during meiosis, one daughter cell would carry a chromosome that had one red- and one green-pigment gene, but the other would have one red-pigment gene and three green-pigment genes—precisely the kind of variation seen in our subjects with normal color vision. There is only a single red-pigment gene in every case because that gene lies at the very edge of the array of color-pigment genes. A gene in that position is highly unlikely to be duplicated (or deleted) by homologous recombination.

Unequal homologous recombination appears to be responsible not only for the duplication of green-pigment genes in people with normal color vision but also for the great majority of deficiencies in red-green discrimination. In collaboration with Piantanida we studied DNA from 25 men who according to Rayleigh anomaloscope tests had variant red-green discrimination. All but one of the subjects had abnormal configurations of red- and green-pigment genes as a consequence of unequal homologous recombination.

Which configurations of genes yield



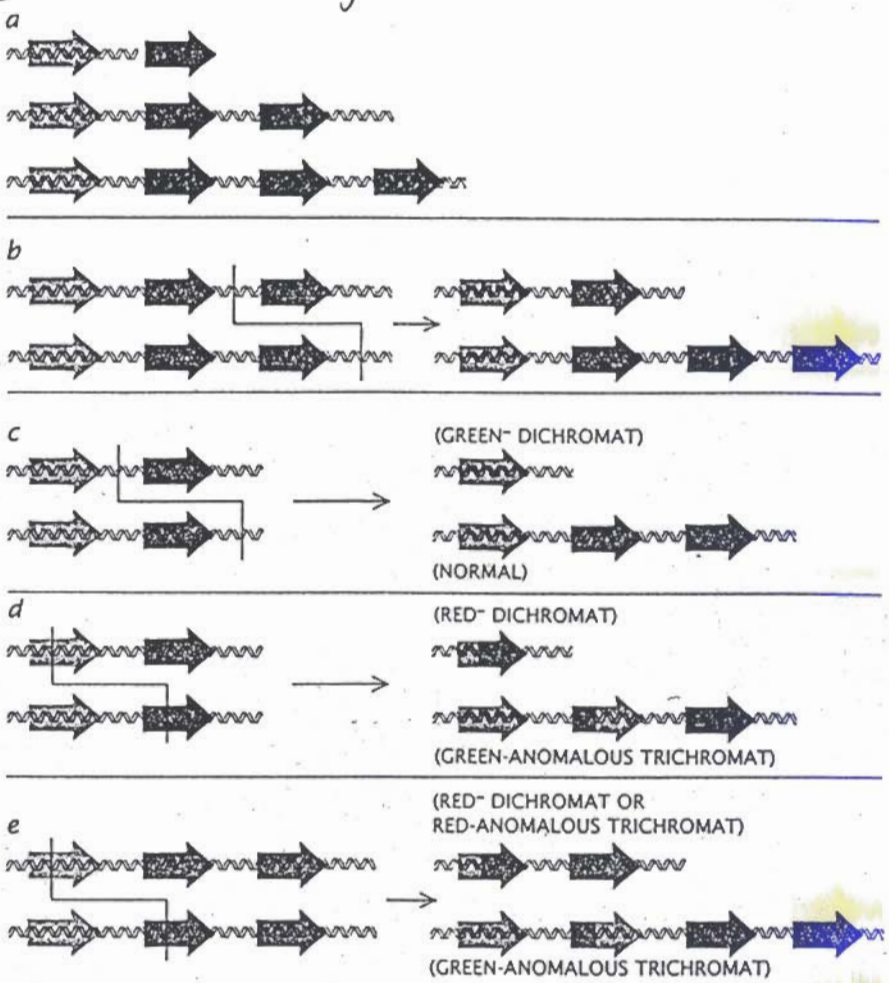
STRUCTURAL COMPARISONS of the four visual pigments on the basis of their nucleotide sequences indicate that rhodopsin and the color pigments all have similar amino acid sequences. (Each colored dot represents an amino acid difference.) The red and the green pigments are most alike; in fact, they are almost identical with one another (*d*). When the molecules being compared have different lengths, the longer molecule is depicted and the unshared "extension" is colored in.

red⁻ or green⁻ dichromats and which produce anomalous trichromats? We found that most of the green⁻ dichromats (those who apparently lacked the green receptor) had simply lost all green-pigment genes. In some green⁻ dichromats, however, the green-pigment gene had been replaced by a hybrid gene: the DNA sequences near the start of the gene were derived from a green-pigment gene and the remaining sequences were derived from a red-pigment gene. Apparently the chromosome with the hybrid gene resulted from recombination in which part of the normal green-pigment gene changed places with part of a red-pigment gene.

Why did the hybrid gene not result in a functioning green receptor? It seems likely that the DNA sequences at the start of either normal or hybrid genes determine the cell type in which the gene will be active, and that the more distal sequences determine the type of pigment produced. This would result in the production of red pigment in cells that would normally become green cones, allowing them to function only as red receptors.

Among men whose Rayleigh anomaloscope tests indicated an absence of the red receptor (red⁻ dichromats), the great majority did not lack red-pigment sequences entirely. Instead their single red-pigment gene had been replaced by a hybrid in which only the initial DNA sequences were from a red-pigment gene. We surmise that this hybrid gene results in the production of a green pigment in cells that would normally have become red cones, in effect endowing people who carry the gene with all green cones and no red ones.

All the subjects with anomalous trichromacy had at least one hybrid gene in addition to some or all of the normal visual-pigment genes. We suppose that in these individuals the hybrid genes encode proteins that have anomalous spectral sensitivities. Our findings suggest that a variety of anomalous pigments are possible and that the particular spectral sensitivities of these pigments are determined by the exact point of crossing-over within the hybrid gene. The larger the fraction of the hybrid derived from the green-pigment gene is, the more greenlike the encoded pigment will be; likewise, if a large fraction of the hybrid is derived from the red-pigment gene, the encoded pigment will be more redlike. If we are correct, our data would account well for the psychophysical observation that anomalous receptors most efficiently absorb wavelengths lying in the interval between the wavelengths that are most efficiently absorbed by normal red and green cones.



EXCHANGE OF GENETIC MATERIAL between normal X chromosomes, which bear the red-pigment and green-pigment genes (*colored arrows*), can give rise to either normal or abnormal red-green color discrimination. X chromosomes derived from normal individuals have one normal red-pigment gene and one, two or three green-pigment genes (*a*). Such normal variation can readily arise when a chromosome with one red- and two green-pigment genes loses one of the green-pigment genes to its mate (*b*). Dichromacy and anomalous trichromacy commonly arise from genetic exchanges that result in the loss of a pigment gene (*c*) or the creation of a hybrid gene derived in part from a red- and in part from a green-pigment gene (*d, e*). The light sensitivity of a hybrid pigment depends on the point of crossing-over within the hybrid gene.

Exciting questions concerning the role of cones and pigments in color vision remain. What is it about the visual pigments that gives them their distinctive absorbance spectra? How does each photoreceptor cell determine which visual pigments to produce? How are connections between photoreceptor cells and high-order neurons formed during development? For those seeking answers to these and related questions, inherited variations in human color vision are a gift, offering a unique window to the inner workings of the eye.

FURTHER READING

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